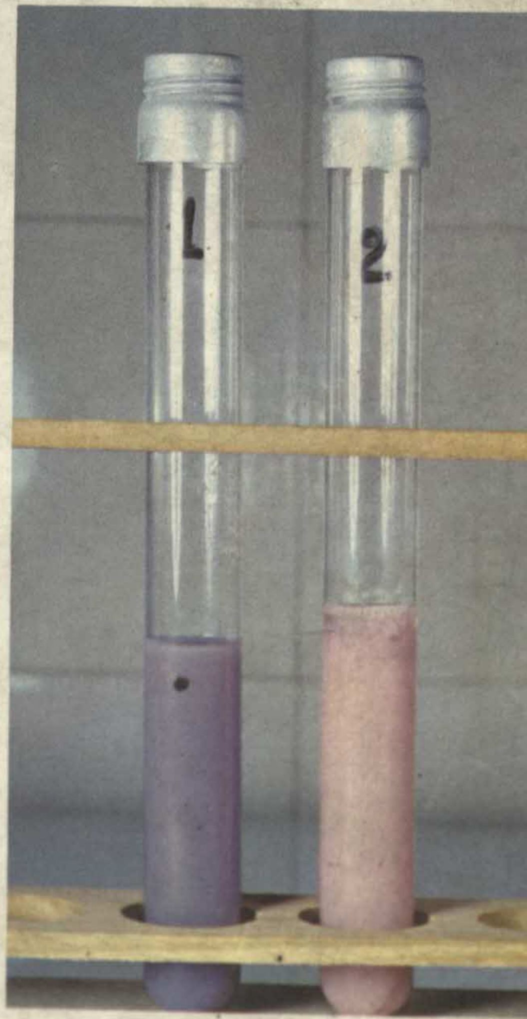

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THE LIVING UNIVERSE

An Encyclopaedia of
the Biological Sciences

The human machine
disorders

THE LIVING UNIVERSE
An Encyclopaedia of the Biological Sciences

With an introduction
by M. F. Perutz, CBE, FRS,
Nobel Laureate in Chemistry

Biology is the science of life—that branch of the sciences which touches everyone most nearly. In the past ten years more striking developments in biological research have taken place than at any other period. The breakthrough which is the key to so much of this work was the discovery in 1953 of the structure attributed to DNA — deoxyribonucleic acid — the chemical basis of the genes which is responsible for the handing down of hereditary characteristics. As a result recent discoveries in biology have been most important and prolific.

Now these momentous discoveries about man and the world he lives in have been collected in eight volumes which will rank among the most important scientific publications of the post-war years. 250 experts from many countries, among them two Nobel Prizewinners, have collaborated to describe the entire range of modern biological and medical research and every manifestation of living matter has been included. The result is a fascinating work, which makes this knowledge available in concise form to the general reader, as well as to scientists in other disciplines.

The unique quality of this publication lies in the combination of some 2,000 magnificent illustrations, 1,500 of them in full colour, with lucidly written texts of the very highest authority. Ranging from the simplest cells to the complexity of man, *The Living Universe* is an exploration in depth of the entire spectrum of life on earth and an introduction to the transformation of man in the world of tomorrow.

Dr. M. F. Perutz writes in his introduction:

'Modern biology has become more like physics, and its new face is reflected in these volumes. Throughout, the emphasis is on the experimental approach rather than on pure observations. Solutions to the great outstanding problems of medicine may well come, not only through a study of man, but also through ingenious experimentation on some lowly species. This encyclopaedia introduces the reader to some of the exciting discoveries made in studies of viruses and unicellular organisms.'

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An Encyclopaedia of the Biological Sciences

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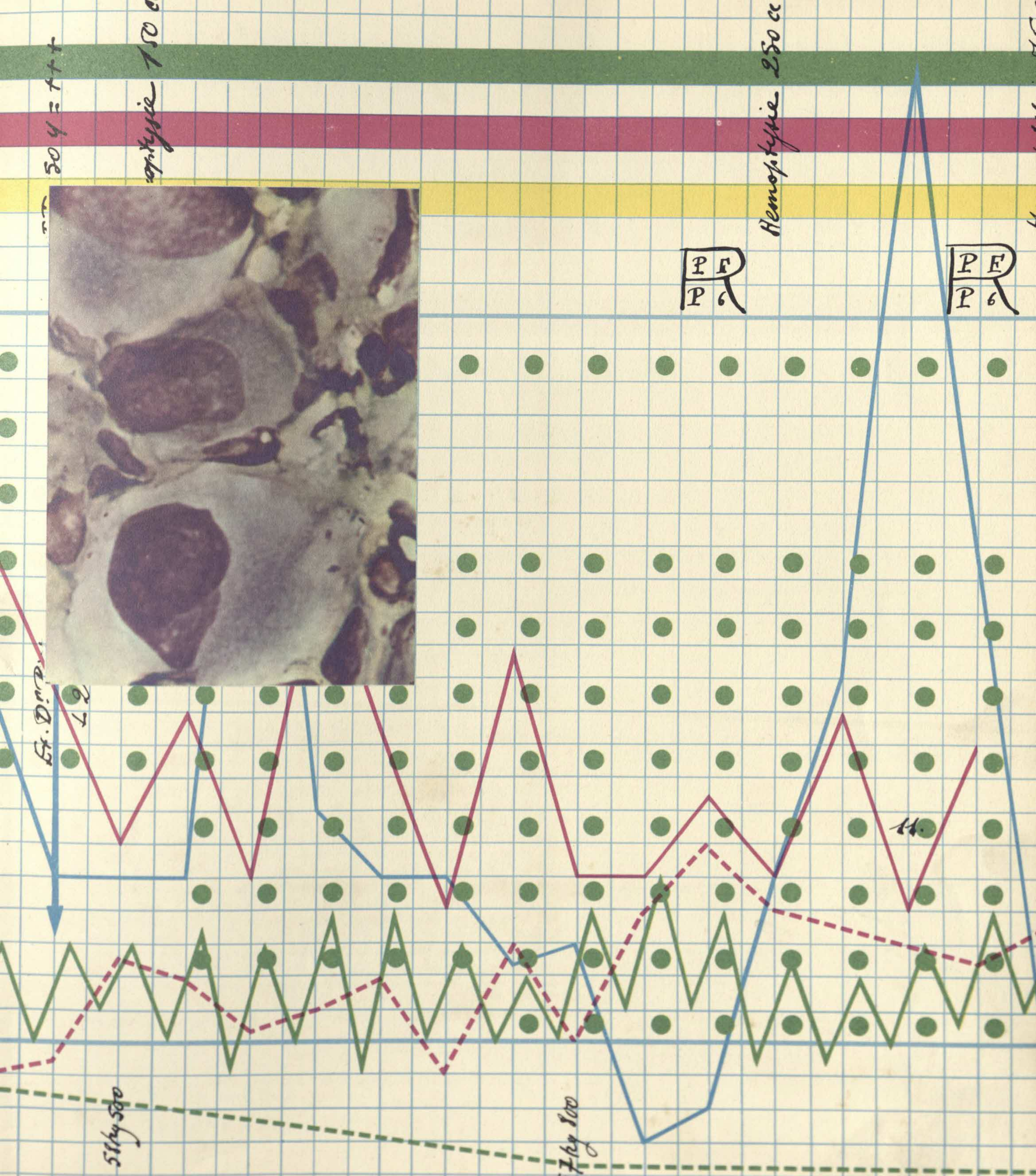
It should be pointed out that the methods of consultation and group discussion between physicians which are referred to in this volume are by way of being experimental procedures that are at present confined mostly to France.

Claude Bernard, the father of modern physiology, has shown that there is no essential difference between living matter that is healthy and that which is diseased. Illness is nothing other than a disorder of the infinitely subtle mechanisms of the human machine. The doctor in the electronic age tends to become an engineer who, after analysis of a machine's behaviour, can re-adjust it so that it achieves its desired performance.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THE LIVING UNIVERSE

An Encyclopaedia of the Biological Sciences

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The human machine: *disorders*

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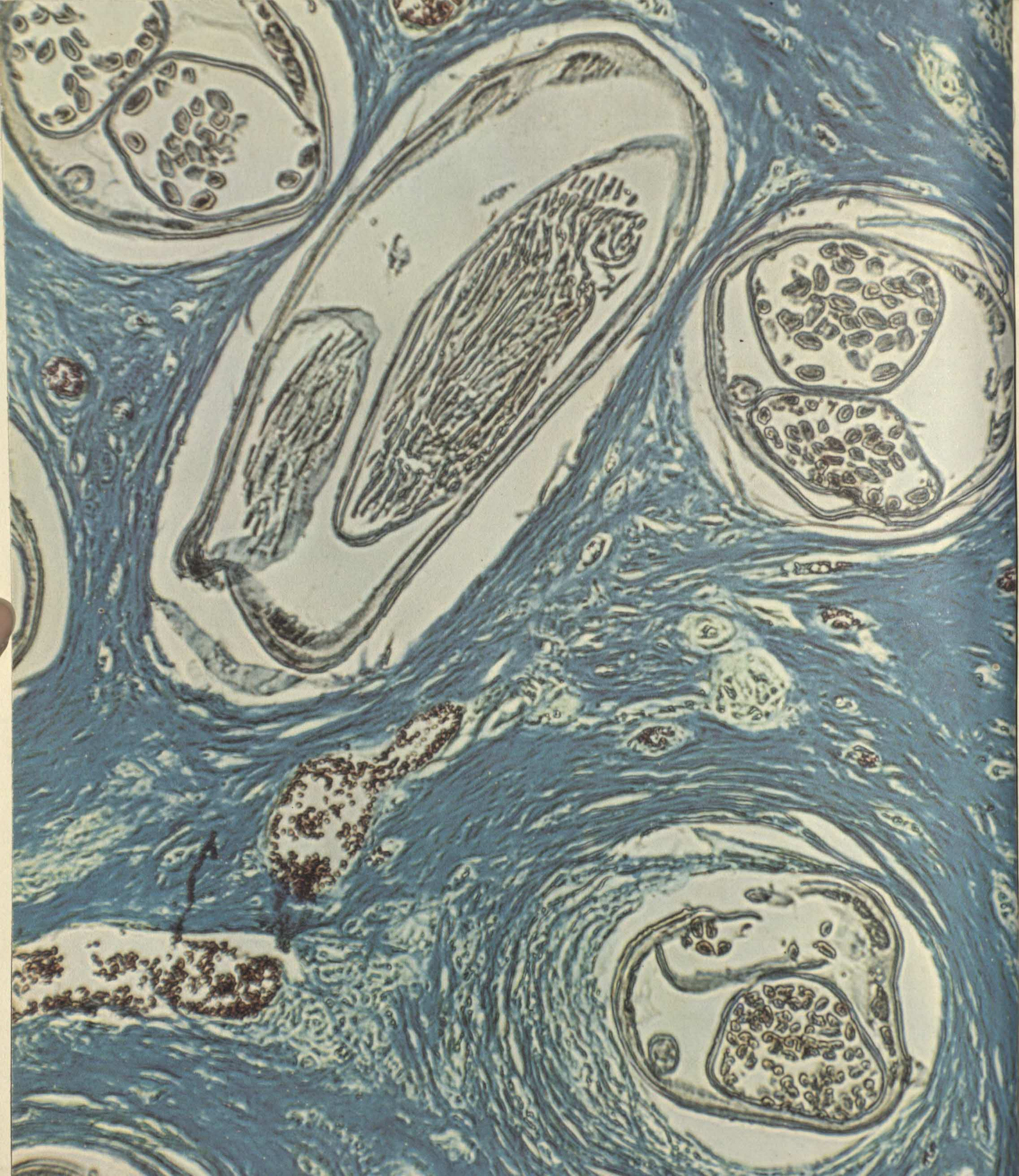


Diseases and disorders

Raoul KOURILSKY

Illness is inseparable from life. It exists in all species, even in bacteria, and at molecular level. As part of the living world, illness is a subject coming within the scope of biology, and must be studied in the same perspective, with the same means, calling on the same sciences, and using the same experimental method that was fashioned by the advent of science. This study must be deep enough to include biochemical and molecular phenomena. It must be approached with an exacting care which demands the use of mathematical means wherever possible and involves the most abstract scientific ideas.

Only recently has this concept been accepted. Over the centuries learned people who tried to study illness had no other means of doing so than to describe what they saw, record what the patient said about his feelings, try to put together the symptoms to make a seemingly coherent whole, treat this collection of knowledge as an entity, and give it a name.

Bichat was the first to resort to anatomy in the widest sense of the word, ie, anatomy as the study of the forms and functions not only of organs but of tissues as well. Everywhere in Europe this path was explored with enthusiasm. The truth was sought in the correlations between symptoms and lesions. This systematic comparison, in which Laënnec excelled, gave the investigation of disease a solid foundation. It firmly established the concept of 'lesion' or 'trauma'. The study of symptoms had to be linked to visible and palpable effects on organs. It appeared from these studies that lesions of extraordinarily diverse appearance were often due to the same cause. One of the most remarkable examples is that of tuberculosis, which sometimes hardens a whole area of tissue (sclerosis) and sometimes softens and liquefies it (cold abscess); this disease may equally well show itself as a simple organ inflammation which transforms some areas into a sort of compound (caseum) which does not in any way resemble the original tissue.

Another discrepancy was even more disturbing: many disorders did not reveal themselves anatomically. In these cases, some authorities denied that there was an illness at all and even went so far as to say that patients were imagining the symptoms.

Neither the microscope, which brought anatomical observation down to the cellular level, nor the electron microscope, which carried investigation inside the cell to the molecular level, has enabled the anatomical method to be extended to the limits of knowledge. However far developed this method may be, it does not reveal anything about mechanisms.

A decisive change in the concept of disease was brought about by Claude Bernard, when he showed that no difference in kind existed between healthy living tissue and diseased living tissue; thus, the patient could be studied with the experimental method that had already been tested in physiology. Only

Disorders of the human machine are caused, in most cases, by a virus, a bacterium, or a parasite. These are external agents that have entered the body by some means or other. Tuberculosis is a bacterial infection that is diminishing today because an intelligent policy of prevention is being pursued (see photo above) and antibiotics are employed. Virus diseases give more cause for concern, as do diseases caused by animal parasites. These often give rise to tumours and irreversible damage. On the left-hand page is shown a microphotograph (mag. × 266) of human tissue attacked by Onchocerca *or filaria, a Nematode worm. (See details given on page 44. Photo Lod).*

External environment and, even more frequently, ways of living are the cause of other disorders. The part played by cholesterol in arterial sclerosis is well known. Here cholesterol crystals are seen, slightly enlarged in a preparation from a human subject. The disseminated dark spots are red cells. The small white spots are fats. (Photo Dr R. Robineaux).

by the use of such a method could the last secrets of the human machine be revealed; the doctor had to learn to 'use physiology as he would a microscope'.

For the first time, disease was placed in its correct setting—that of biology.

Behind the appearance of lesions, it became possible to reconstitute the linkage of disturbances that determined the symptoms and to act on these by suppressing the initial cause or by intervening at intermediate points. Physiological exploration concentrated the sciences (chemistry, physics, and enzymology) and the techniques on the hypothesis enunciated to explain the disease.

The immense progress made in anaesthesia and surgery is due to the innumerable physiological discoveries used in attacking the problems of pathology; the same is true of the extraction and synthesis of organic products, notably internal secretions, which are universally employed in medicine.

For a time, physiology as a means of acquiring knowledge was eclipsed by the extraordinary discoveries of Pasteur and his successors in bacteriology. Their identification of the infectious agents, bacteria and viruses, revolutionized medicine. Thereafter, symptoms and lesions could be explained by penetration of the human organism by a foreign body, and disease acquired its character and identity from the infecting agent. The disease could thus be eliminated by attacking the unwanted host, either during its transmission, penetration, or parasitic life inside cells and tissues of the organism. This is nowadays achieved by using antibiotics.

The striking successes obtained by vaccination and antibacterial treatment cut short controversy. Naturally, it was hoped that most disorders would be traceable to outside invasion, and many assumed that it was merely a matter of finding the invader. Many disease conditions, attributable to other causes, were falsely attributed to invasion by living agents.

Knowledge of bacteriology revolutionized the prevention of disease. It rid the human species of infestation by environmental parasites. It completely changed health measures, and by so doing introduced other benefits. It gradually became apparent, however, that the concept of disease had not been as radically transformed through bacteriology as had been imagined.

It had been shown that the transmission of an infective agent could occur without any consequent specific illness. Healthy yet contaminated persons thus spread diseases of which they showed no symptoms. The discovery of germ carriers and of 'inapparent diseases' (to borrow a phrase of Charles Nicolle) showed that an organism could continue its functions although all the conditions of infestation might be present.

These facts led to the discovery of a whole series of specialized physiological systems for protecting the organism. They formed the basis of a new science which is still being developed today—immunology, of which Roux was the precursor.

Orders and disorders

A visible and palpable illness represents what may be described as only more or less lengthy a stage in a biological disorder that has already begun and may or may not last beyond apparent recovery.

Before lesions occur, there are functional disturbances. Leriche was one of the first to show that such disturbances occur in the small vessels. Understanding of the disease must, therefore, go beyond the lesion, beyond the isolated functions of organs, to the identification of disorders occurring before the disturbances establish themselves.

Once again we are indebted to Claude Bernard, who defined the object of regulation as: *maintenance of the constancy of the internal environment*. In each place, at each moment, and, in the right proportions, each cell must have the exact conditions required for its life. To attain this state of perfection, the unceasing fluctuations arising from inside or from outside must be strictly compensated.

Each of the conditions essential to life is therefore subject to precise regulation, in which many organs all over the body participate. Equilibrium is obtained by the interplay of two contradictory forces, the one stimulating, the other inhibiting.

A quantitative analysis of this regulation has been made recently by Pierre Vendryès.[1] It embraces two essential stages: placing in reserve and putting into controlled circulation. The latter is effected by the general mechanism of feed-back, described in cybernetics by Wiener. Regulation takes place according to the difference between the physiological norm and the deviation from it.

Proportional and integral action have been found in the human organism by Vendryès; these are known in cybernetics and used every day in the construction of regulating machinery.

This form of research opens the way to

mathematical correction of organic adjustments. The constancy of the internal environment allows the organism to escape from direct dependence on the external environment. The organism acquires physiological autonomy.

Any damage to these adjustments, providing it is profound enough and sufficiently long-lasting for compensation to be no longer effective, determines the appearance of a disease. At first the disease is purely biological, but sooner or later it reveals itself, sometimes insidiously, sometimes suddenly.

There is no disease without some damage to adjustments, whether as a preliminary or during the course of development. Many acquired diseases are implanted and become rooted or aggravated only because certain basic adjustments are attacked. The nervous system plays a fundamental part in regulatory adjustments. As regards motor movements, sensitivity, reflex co-ordination of movements and balance, the integrative action of the nervous system is built into the anatomy.

The basis of visceral nerve correlation is much less clear. Pathology rather than physiology has revealed the importance of this correlation. Though the role of mental factors has only just become apparent, it is nevertheless fundamental. Here it is the emotional changes that have repercussions on the organs.

We are still ignorant about this psychological and biological regulation, the proper functioning of which is a major condition for health. But we do know that damage to it causes and prolongs disorders that are exactly like organic diseases. This well explains disorders which no apparent lesion justifies, and which afflict most of mankind.

Over and beyond the lesions, but before getting to the damage done to the functions, the aim of all research into disease must now be to discover disturbances in the adjustments.

The internal causes of disorder

There are certainly many diseases yet to be identified. Among those that are recognized are many of which the causes are unknown. Some develop in man throughout the whole of his life.

These gradually developing diseases seem to be linked to bad functioning of the internal machinery; for example, degenerative osteoarthritis, high blood pressure, atherosclerosis, diabetes, and gout.

Such conditions are thought to arise from disorders in the way in which the cellular enzymes work together. It is known that individuals are unequally affected, which implies a distant genetic influence.

The only internal disorders that are known with some precision are what are called inborn errors of metabolism. They depend on the presence or absence of certain genes, ie, tiny amounts of deoxyribonucleic acid, making up the chromosomes within the cell nucleus. Damage to even one of these genes is reproduced over the generations and at the same place on the molecular chain, in conformity with the general laws described by Mendel.

Disease results in these cases from the physiological influence of the gene on the organism.

A number of genes govern certain stages of metabolism, eg, the transformation of galactose into glucose and the synthesis of glycogen in the liver. They give the cells the required information, so that they may produce the essential enzymes: p-galactose transferase, glucose-6-phosphatase and amylo-1-6-glucosidase, which intervene respectively in the synthesis and break-down of glycogen. Other genes affect the nitrogen metabolism. For example, in the absence of a special hydroxylase, the amino acid phenylalanine can no longer be broken down. It accumulates, phenylketone appears in the urine, and simultaneously, considerable mental disturbances occur.

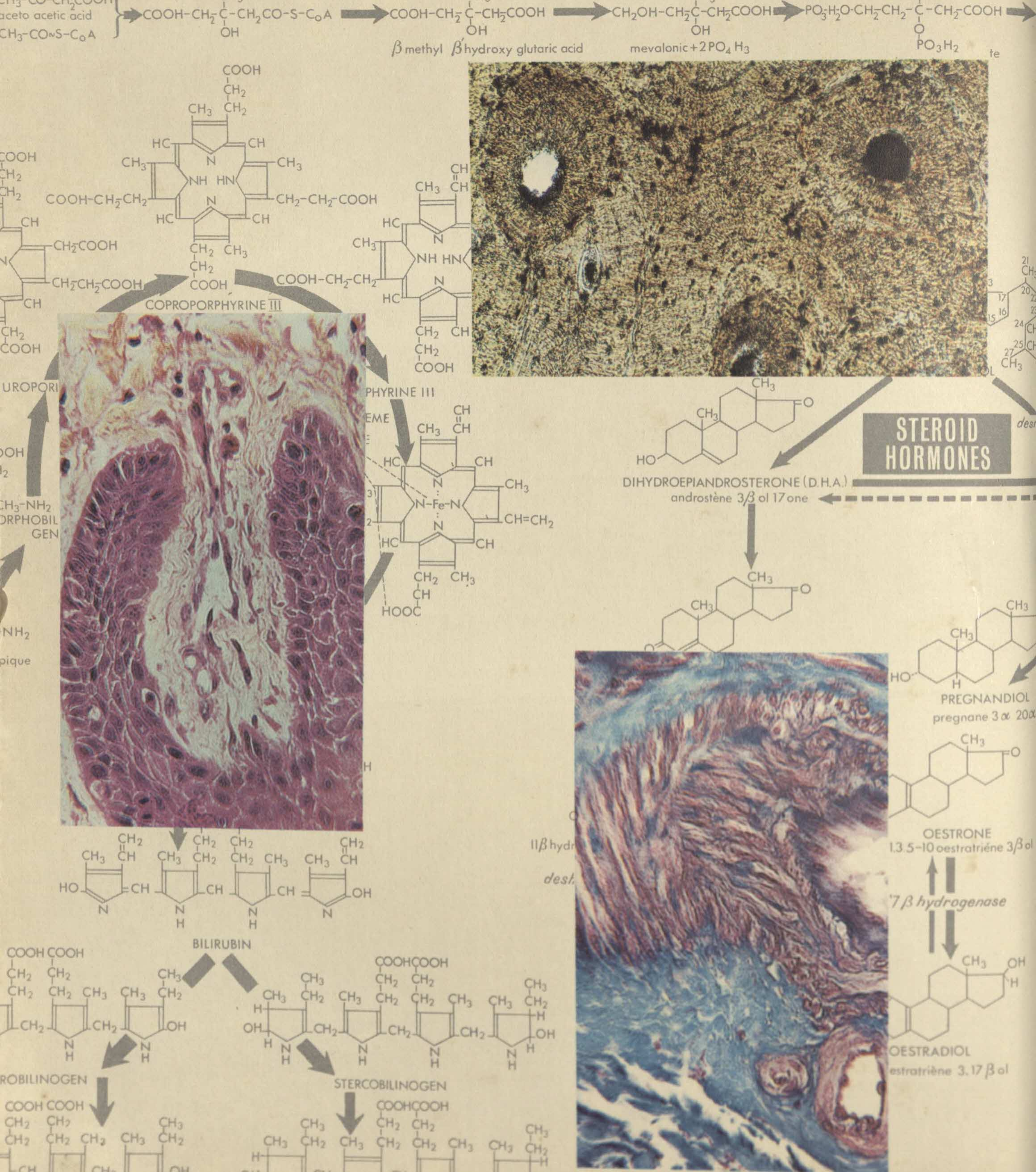
Many mysteries remain to be solved in this field, but as experimental biology continues, so will the body's regulatory system give up its secrets.

Influence of the external environment

Many diseases arise from the penetration of the organism by foreign substances. The frequency of these harmful introductions is indeed very high. Bacteria, viruses, mycelial spores, and unicellular and multicellular parasites surround us on all sides and penetrate our bodies in the most subtle ways.

Air is an inexhaustible source of disease. Septic contamination of airborne origin occurs especially when air is humid. The smallest droplets adsorb bacteria and viruses. All winter illnesses—pneumococcal and streptococcal infections as well as influenza—are transmitted in this manner. Diseases of an epidemic nature may be caused by mycelial spores introduced by breathed-in air. They simulate epidemics because a great number of persons are infected at the same time. Wind may transport spores considerable distances and create new

On the next page: *living tissue appears under the microscope as a mass of splendid forms and colours which conceal the complexity of its chemical workings. Living activity is a series of reactions, using enzymes as catalysts, which the biologist attempts to outline in complicated diagrams. Certain aspects are shown here: on the left, synthesis and degradation of haemoglobin; in the centre, the hormone cycle; on the right, the Krebs' cycle. The sections show, from left to right and from top to bottom, skin papillae, bone tissue, skin epithelium, mucous glands of the digestive tract, brain matter, sweat and glands. (Photo Lod).*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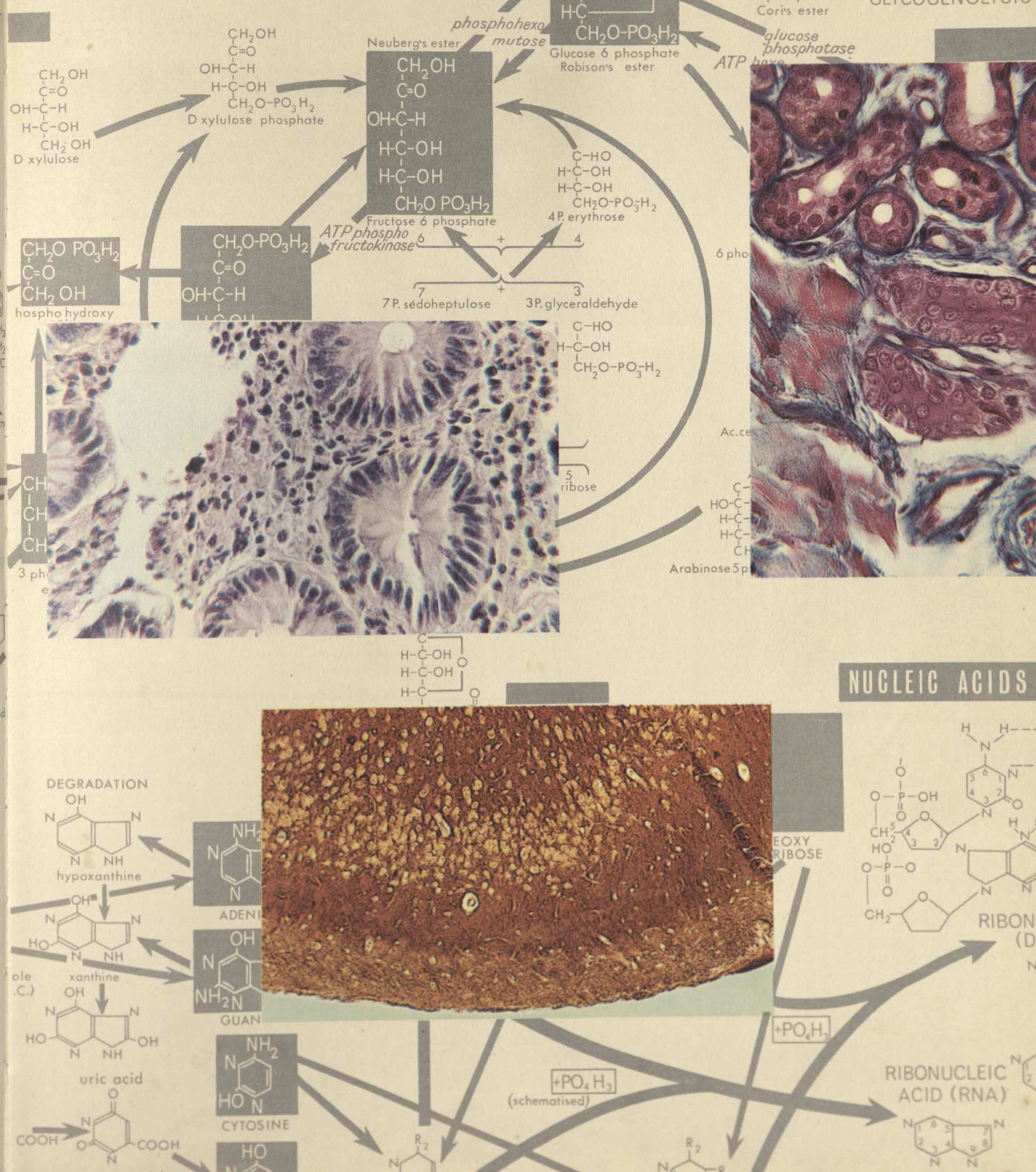
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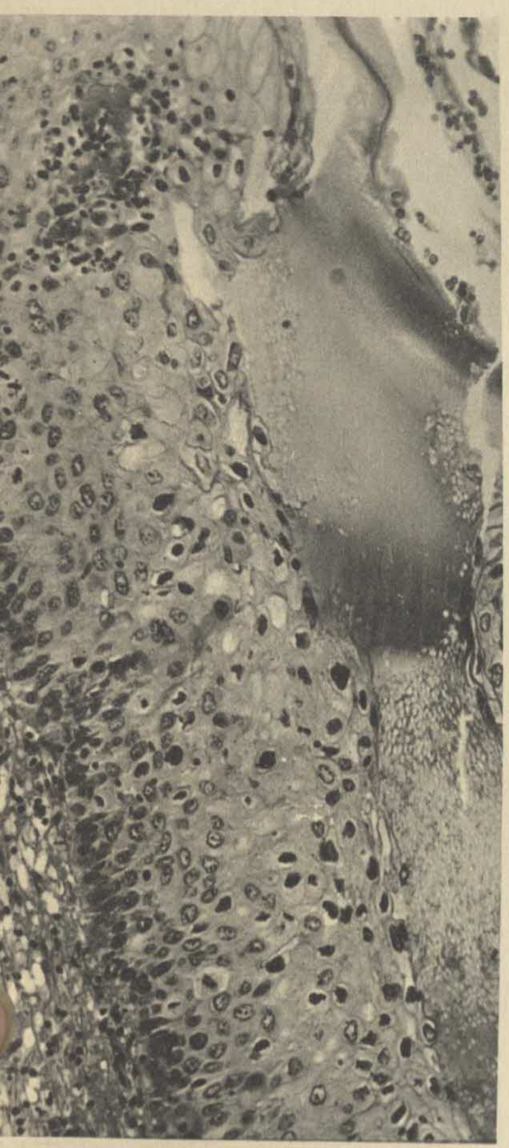


Some disorders are of unknown aetiology. Such is the case of this proliferation, called cancer. The microphotograph shows the appearance of an epithelioma of the neck of the uterus: the limit between healthy and cancerous tissue may be seen here. (Photo Dr R. Robineaux).

foci of infection. An example is coccidioidomycosis, a new disease, which has been identified in the United States (San Joaquin valley fever).

The second natural element of life, *water*, is also a vector of diseases. The best known are bacterial, such as the salmonella infections, of which the species *eberthii* causes typhoid fever, cholera, and dysentery. Water also transmits viruses, particularly those of poliomyelitis, hepatic spirochaete and an important number of parasites such as dysenteric amoebae, liver flukes and many others. Transmission may be direct or indirect (eg, by means of washed vegetables).

Some pathogenic agents may penetrate directly through the skin or healthy mucosa; examples of these are the gonococci or the treponemes.

Any contact the organism has with apparently inert particles—usually through the medium of the atmosphere—may be extremely harmful. A case in point is the mineral particles inhaled by miners and tunnel workers. The lungs take in these particles and their chemical activity creates and maintains inflammatory nodules indefinitely. In this way, 'dust diseases' develop; the most serious of them is silicosis. Such diseases often appear to occur spontaneously because lesions form only after many years' exposure.

Inhaled dusts from vegetation may cause harm by means of a mechanism other than that of direct chemical action. Captured by specialized cells (after penetration into the internal medium), they set in motion the manufacture of antagonistic substances called antibodies. These react in the mucosa of the lungs with newly introduced particles and liberate irritating substances such as histamine, which cause asthmatic symptoms. This is the mechanism of hypersensitivity induced by aerial means. The possibility of a harmful effect of an external environment must always be borne in mind.

This effect may be extremely subtle. For instance, if the atmosphere at the place of work contains minute proportions of acid or alkaline irritating vapours, and if inhalation of these substances is renewed daily during a period of life, the terminal bronchi are partially obstructed and contract or collapse. They lose their essential function, that of guiding air towards the larger bronchi on expiration, and the lungs can no longer expel it; the result is emphysema, with formidable effects on lung circulation and on the heart.

If drinking water is deficient in iodine (20 to 200 thousandths of a milligram per day are normally required), the thyroid gland can no longer secrete thyroxin in sufficient quantity. A whole series of disorders then occurs: growth is no longer maintained; bone development is retarded; the anterior pituitary increases its secretion to encourage thyroid secretion, and the gland enlarges to form a goitre.

The absence of certain microconstituents of solid food also leads to very serious diseases. While investigating what was apparently an epidemic disease on English mail-boats, James Lind discovered, in 1753, that scurvy was of dietary origin. It was much rarer among officers and their servants than among the sailors, because the former had the privilege of eating certain vegetables and fresh fruit, either in port or at sea, besides the normal diet of salted preserves, which do not contain certain essential accessory food factors.

Today, more than thirty of such substances, called vitamins, are known. They regulate metabolism and the exchanges that occur in it. They cannot be replaced, and in their absence certain functions cannot take place. For instance, the chemistry of vision and the health of mucous membranes are strongly affected by vitamin A. In the absence of nicotinic acid (a vitamin of the B group), respiration of the tissues is affected because dehydrogenation and the transfer of hydrogen can no longer come about; many disturbances appear, including mental and nervous ones (pellagra).

One example of the intricate relationship between bacteria and human life is illustrated by the fact that certain bacteria living in the intestine play the role of synthesizers of vitamin K, which is connected with blood coagulation and cannot be made by the human organism. If these bacteria are destroyed by antibiotics, serious consequences may ensue.

When a diet consists of 800 calories per day (instead of 3,500) and 40 grams of protein, as it may in under-developed countries, the least variation in the protein intake (meat, for example) becomes very important. It has recently been shown that among African Negroes, who do not drink alcohol, protein deficiency leads to cirrhosis of the liver. Water is no longer retained; it invades the limbs. These famine diseases occur as epidemics in autochthonous populations and are now known under the name of *kwashiorkor*.

Man, however, has also the power of voluntarily impairing his diet and of upsetting its balance by the introduction of alcohol. If a man's alcohol intake is great enough, his body may develop serious nutritional disorders (such as cirrhosis of the liver), nerve disturbances (paralysis), and psychological disturbance *(delirium tremens)*.

As any alteration of environment may affect man, it is impossible to study the human organism independently of this. The action of psychological environment on man is of extreme importance in the development of a human being. A child is conditioned by those around him, and the influence of both his parents is essential for his emotional development.

The non-adaptation of the adult to the psychological environment in which he must live not only leads to serious psychological consequences but, through affective disturbances, it also causes visceral disorders, which may become the point of departure of fixed organic modifications.

Disease and health

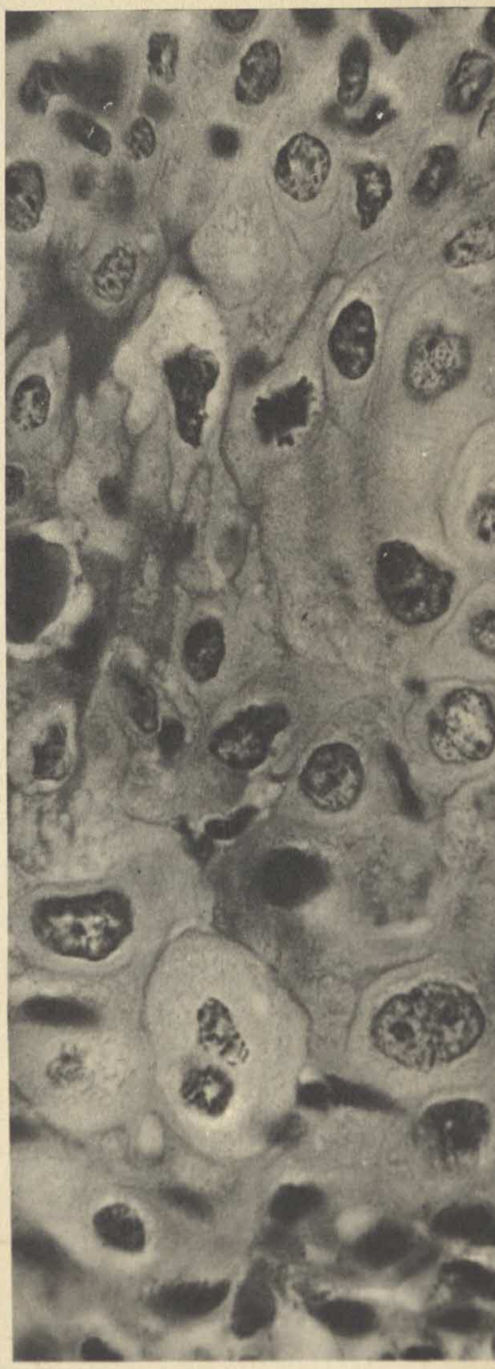
It is apparent from our discussion thus far that a knowledge of disease is no longer exclusively descriptive. It must be scientific, in the sense that not only the lesions but also the functional disturbances that maintain them must be discovered. It is quite remarkable that this idea, which has been laboriously developed after nearly a century of experimental science, is already included in the traditional definition of health and disease.

Disease can indeed be defined only with reference to health. According to Littré, a sick person is one whose health has been reduced. 'Health is the state of someone who is healthy . . . it is the permanent and easy exercise of all the functions of the economy.' Health involves a very great degree of regulation, vigorous adjustment of mechanisms, and implacable conditioning of reciprocal adaptation.

The term 'malady' derives from the Latin *male aptus*. *Aptus* signifies 'linked', 'adjusted'. A malady or a disease, therefore, is a state contrary to that of health, being one in which the exercise of functions is neither easy nor permanent, since the economy of the body is not adjusted.

If all functions are exercised within their normal limits and if they are exactly coordinated, a man is in good health. He does not have to worry about his appearance or constitution. Disease is the result of maladjustment of functions, whatever the cause. In order for recovery to be achieved, this maladjustment must be found and corrected, regulation must be re-established and the whole organism brought into line.

More and more, the doctor's approach to disease must be that of a biologist. He can no longer learn from books. Every day there must be a closer correlation between biology and medicine. The more this movement gains momentum, the more striking will be the progress of medicine. The experiences of the last few years leave no doubt about future successes as long as the science of disease works with the same methods, rigour, and rhythm as biology, the science of life.



Enlargement of part of the photograph on the previous page. The middle of the cancerous area is shown. The numerous atypical cells are to be noted. These are characteristic of the most serious of human disorders. (Photo Dr R. Robineaux).

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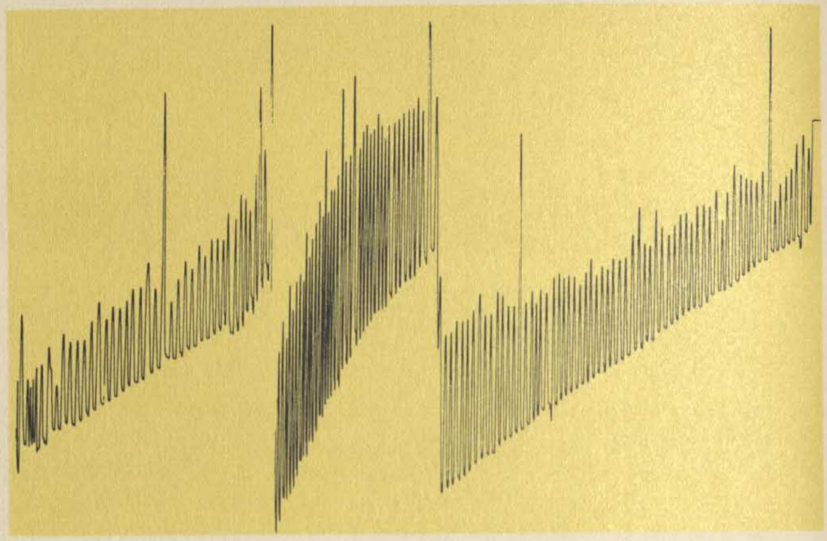
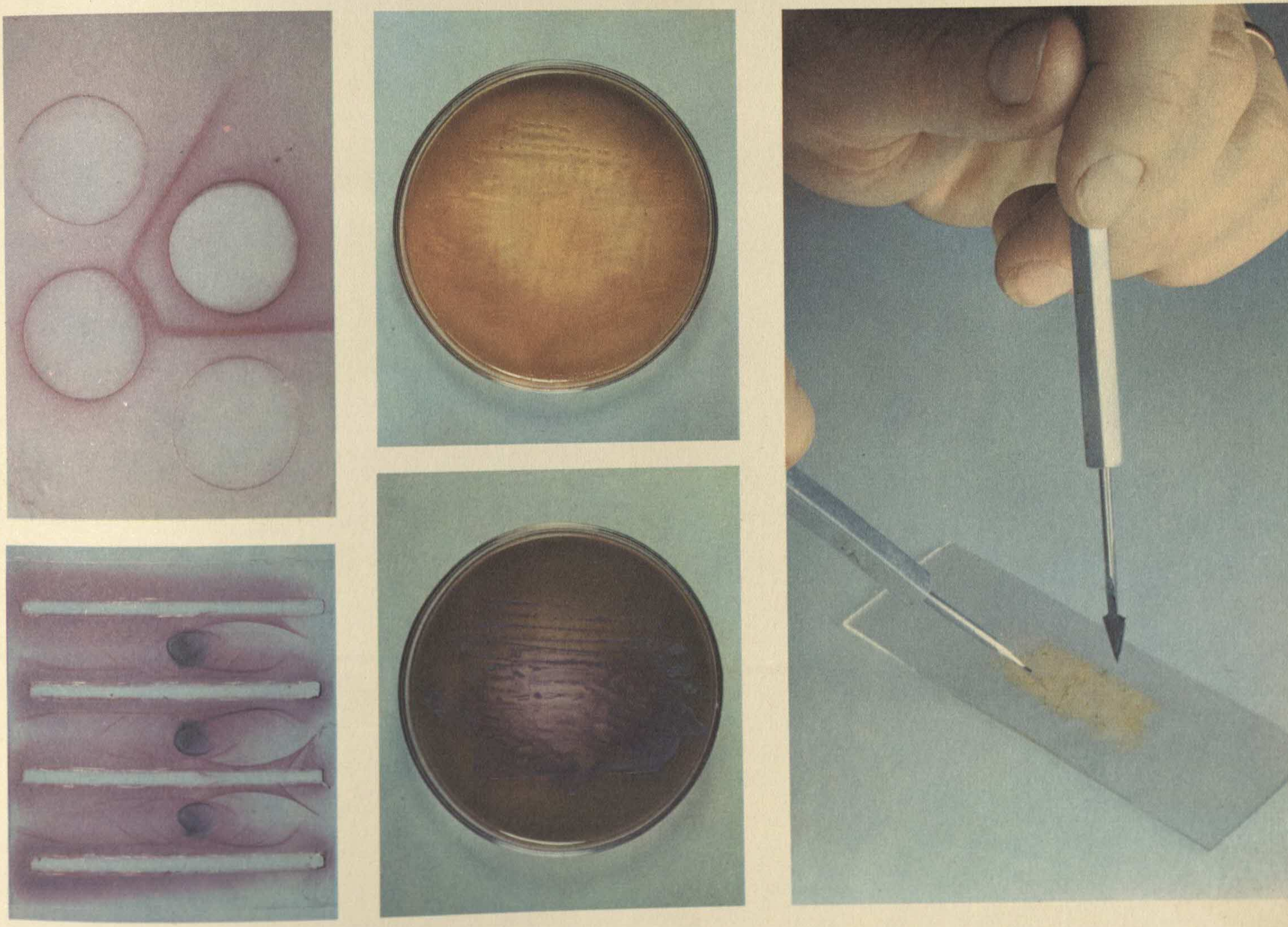
(1) *See the chapter on 'Correlations between Organs', by Pierre Vendryès in the preceding volume, p. 155.*

PART ONE



Acquired diseases, as opposed to organic, tissue and cellular disorders, are those transmitted by infectious agents such as viruses, bacteria, and vegetable or animal parasites. After having examined the patient in the usual way (on the left), the doctor adopts certain techniques in order to reveal and study the diseases further. Some of these techniques are

Acquired diseases



shown above: from top to bottom and from left to right are a spirograph curve (recording of respiratory exchanges); two tubercle bacillus reactions in a rabbit; two illustrations of immuno-electrophoretic analysis designed to isolate various proteins in a physiological liquid; two colibacilli cultures in Petri dishes; and the placing of a histological section on a glass slide. (The photos of tubercle reactions and colibacillus cultures, from the Institut Pasteur at Garches; those showing electrophoresis, from the Institut National du Cancer, Dr Burtin's department; and the photo on the right, from the Hôpital Saint-Antoine, Professor Kourilsky's department. Photos Lod).

Pathogenic microbes

Albert DELAUNAY

Pathogenic germs that cause infectious diseases often exist in the soil or the atmosphere in latent form, not becoming dangerous until they develop inside an organism. This is the origin of microbial diseases which are usually transmitted from one person to another. This chapter deals with different routes of access, the localization and characteristic symptoms of infectious diseases, and finally, problems raised by the mode of action of bacteria and viruses, and also spontaneous recovery.

Bacillus cereus during lysis: bursting and disintegration of the spore body. (Mag. × 18,000; electron microphotograph from The Bacterial Cell *by F. Scanga).*

Some germs pathogenic to man or animals normally exist in the soil. Examples of these organisms are anthrax, tetanus, and those anaerobes responsible for gas-gangrene illnesses. But this is a very exceptional situation linked with the ability possessed by these germs to develop a resistant form, usually called a spore. The great majority of pathogenic bacteria cannot do this. Therefore they quickly disappear from an environment that does not suit them. They are victims of competition from innumerable saprophytic bacteria, fungi, and moulds in their vicinity.

The atmosphere is another habitat for pathogenic bacteria. Here are found, for example, *subtilis* bacilli, streptococci, staphylococci, and even tuberculosis bacilli. In general, the more stuffy an atmosphere is, the greater the number of germs that survive in it. Mists and fogs have a harmful action: the tiny drops of water of which they are made up help to deposit microbes on foodstuffs. Sunlight is, on the contrary, a powerful sterilizer.

A pathogenic germ may cause an infection in animals or in man after having been in the soil, or more probably, in the atmosphere, for some time. However, this mode of contagion is not the most frequent. More often, contagion occurs directly between animal and man, or between man and man. Those who are already infected (whether detectably or not) represent, in nature, the main reservoirs of dangerous germs. We shall now examine the way in which these germs pass from infected subjects to those hitherto immune to them.

Different routes of infection

There are cases of some importance where such a passage is explained by auto-infection. Unknown to himself, a man may carry staphylococci and streptococci on his skin. If he cuts himself, the germs soon enter the wound. They then emerge from their state of quiescence and begin to multiply. They can give rise with astonishing rapidity to a whitlow, an inflammation, or a carbuncle.

At other times, a slight abrasion, only just visible on the skin or mucous membrane, may enable micro-organisms to penetrate deep inside us. This is the route generally chosen by the syphilitic treponema. A deeper wound, especially if it becomes dirty from contact with the soil, may permit the passage of sporulated germs. Finally, bites may inoculate man with formidable infections such as rabies.

Other equally important routes of infection are those of the digestive and the respiratory systems. Infections are mostly conveyed along the digestive tract in water, milk or food. The germs so carried may be the bacilli of typhus, paratyphus or dysentery; the cholera vibrio; a number of viruses, especially the poliomyelitis virus; and *Brucella melitensis, B. abortus and B. suis.*

Grouped under the name of *Brucella*, these organisms are responsible for infectious diseases in goats, sheep, and cattle; in the latter, they lead to epizootic abortion, a disease that may have serious economic consequences. *Brucella* bacteria may be transmitted to man by ingestion of milk from sick animals, or fresh cheeses made from such milk, or by contact with infected animals, carcases, or manure. Contamination by the other germs mentioned above may occur through drinking water or eating raw vegetables that have been watered with infected water. Numerous cases have been reported where the pathogenic germ began to show its presence after the eating of shellfish (oyster beds are often located on sea coasts near sewer exits). Flies are also important carriers of pathogenic microbes.

We have already mentioned that quite a number of pathogenic germs are to be found in the air we breathe. In this case, the natural entry into the organism is through the respiratory passages. The propagation of bacteria and viruses takes place through droplets of saliva, particles of mucus which infected persons spread while talking or coughing. Among the bacteria transmitted in this manner are the different types of pneumococci. But it is also essentially through the respiratory passages that pulmonary tuberculosis of adolescents and adults is propagated.[1] The list of viruses that could be mentioned is even longer; the larynx and lungs appear to be the entry and exit most often used by viruses of the common cold, epidemic influenza, measles, smallpox, poliomyelitis, etc.

A word also needs to be said on another means of propagation which is likewise of great importance: the arthropod. Infection occurs when insects, after biting diseased subjects, then bite healthy subjects. Plague, caused by Yersin's bacillus, is normally a disease of rats and other rodents which is transmitted from one animal to another and from animal to man by flea-bites. When man is infected, a swelling appears in the lymph node draining the area where the bite occurred (this adenitis is called a bubo). When death takes place, it is usually due to generalized infection (septicaemia). But in cold climates death may be the result solely of an attack of broncho-pneumonia. The yellow fever virus is transmitted by mosquitoes. In tropical cities, it is spread from man to man by the bite of the *Aedes* mosquito; in the jungle, it is apparently transmitted from monkeys, which are natural reservoirs of the virus, to man, by the bite of different species of mosquito. The agent of epidemic typhus, called *Rickettsia prowazekii*, is spread from man to man, as was shown by Charles Nicolle, through the intermediary of the flea. Besides epidemic typhus (the historical typhus), there is a variant called rat typhus. Here, the pathogenic germ is carried by rats, natural reservoirs of the virus, to man by means of fleas and from man to man by lice.

Where is the infection localized?

When an infectious disease breaks out, it may give rise either to localized suppurative phenomena or to a more generalized effect on the organism.

These suppurative phenomena are nearly the same, whatever the causative germs (staphylococci, streptococci, or anaerobes). But, of course, the extent and gravity of the lesions may vary widely from one case to another. It is easy to imagine all the gradations between a simple whitlow and a large boil on the arm.

Generalized phenomena result from an initial dissemination of the germs in all the organs and tissues. Generalization, though, lasts only for a limited time. Before long, the germs having been spread through the nerves (as in the case of rabies, herpes, vaccinia) or through the blood (measles, yellow fever, typhoid fever), show a distinct tendency to settle in a single tissue or organ.

Often, the tissue affected is the skin, as, for example, in eruptive fevers (measles, smallpox, typhus, scarlet fever). In other cases, an attack on the intestinal tract is the dominating feature. The affected area may be the small intestine (cholera, typhoid fever) or the large intestine (forms of dysentery). Certain viruses, such as those of colds or influenza, have a predilection for the respiratory apparatus. The virus of yellow fever tends to settle in the liver, and the mumps virus in the parotids or the testicles. A number of agents, such as those of encephalitis lethargica, poliomyelitis or rabies, are localized chiefly in the nerve centres.

Symptoms of infectious disease

In all infectious illnesses, *general* symptoms are much the same: fever, prostration, tiredness. But *functional* symptoms depend on the site where the germs are to be found or will eventually be found. For example, an intense diarrhoea characterizes cholera and dysentery diseases. Coughing is the main symptom of affected respiratory passages. A lesion of the

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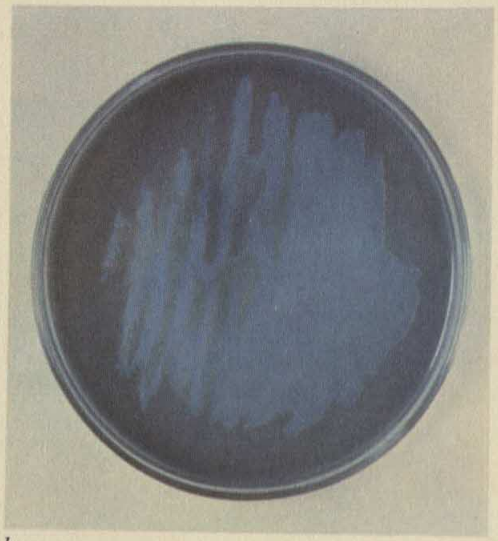
(1) *Here, however, intestinal entry must not be wholly excluded.*

Bacteriology in

After a sample has been taken at the patient's bedside, the bacteriologist cultivates the organism in order to isolate and identify it. The appearance of the germ culture is often sufficient for bacterial identification, but only under a microscope can this be made with certainty. (All the photographs were taken at the Institut Pasteur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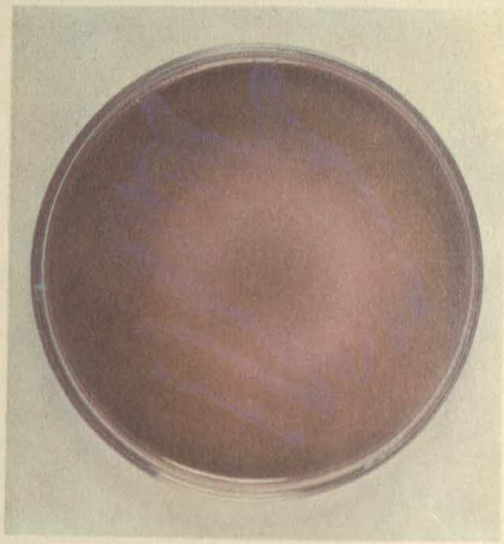
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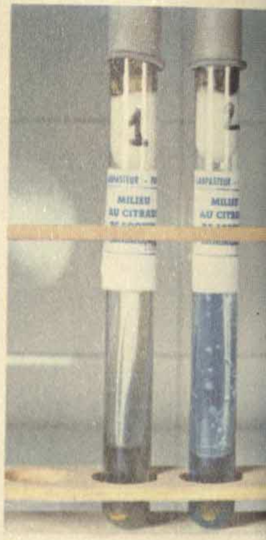

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a. Mycobacterium phlei *in a culture two months old at 37°C in Lowenstein's medium. b. Eosine medium, methylene blue stain, typhus bacillus, small grey colonies, medium unchanged. c. Dricalski's medium, typhus bacillus, greenish colony, unchanged medium. d. Simmons's medium (sodium citrate): 1. colibacillus: citrate⁻ (the medium remains green, there is no culture and no change); 2. proteus: citrate⁺ (the medium turns blue, culture takes place). e. Differentiation between colibacillus and typhus bacillus by studying biochemical characteristics (glucoside fermentation). f. Typhus bacillus. g. Fermentation and change of coloration. h. Microscopic observation.*

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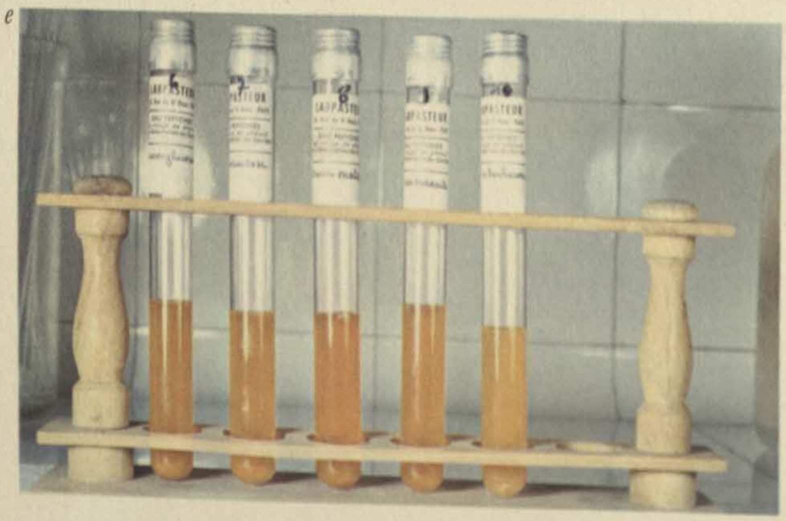

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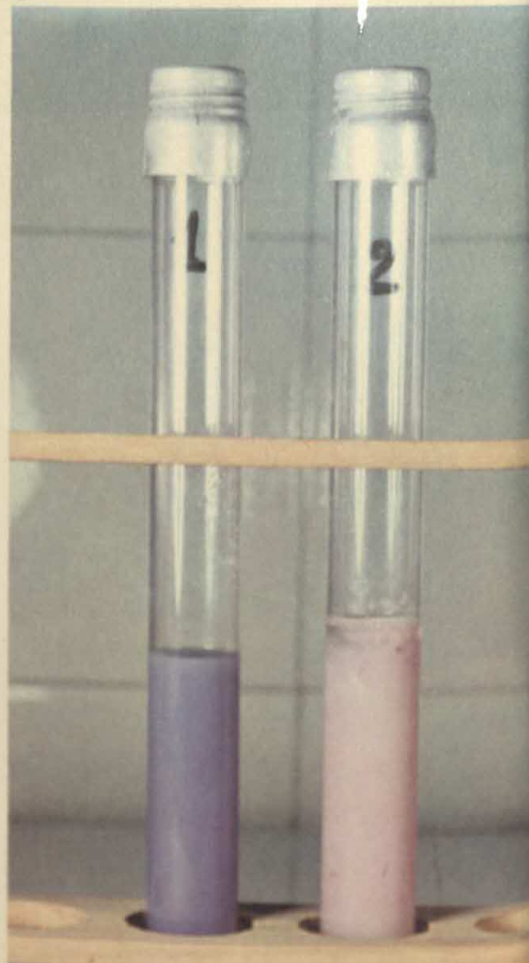

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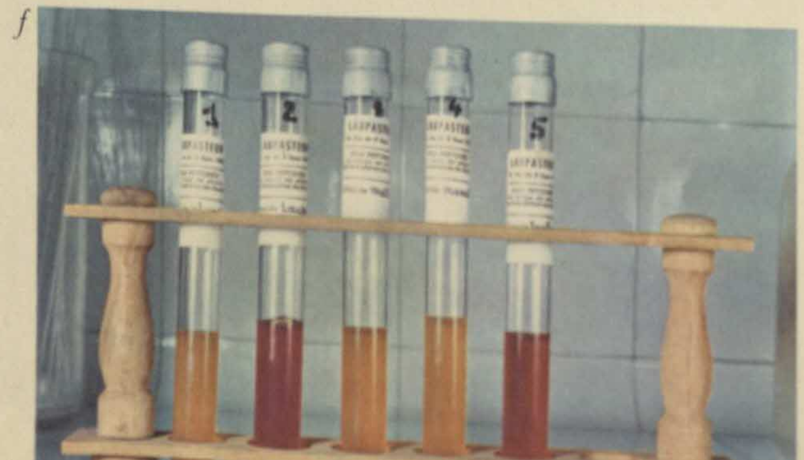

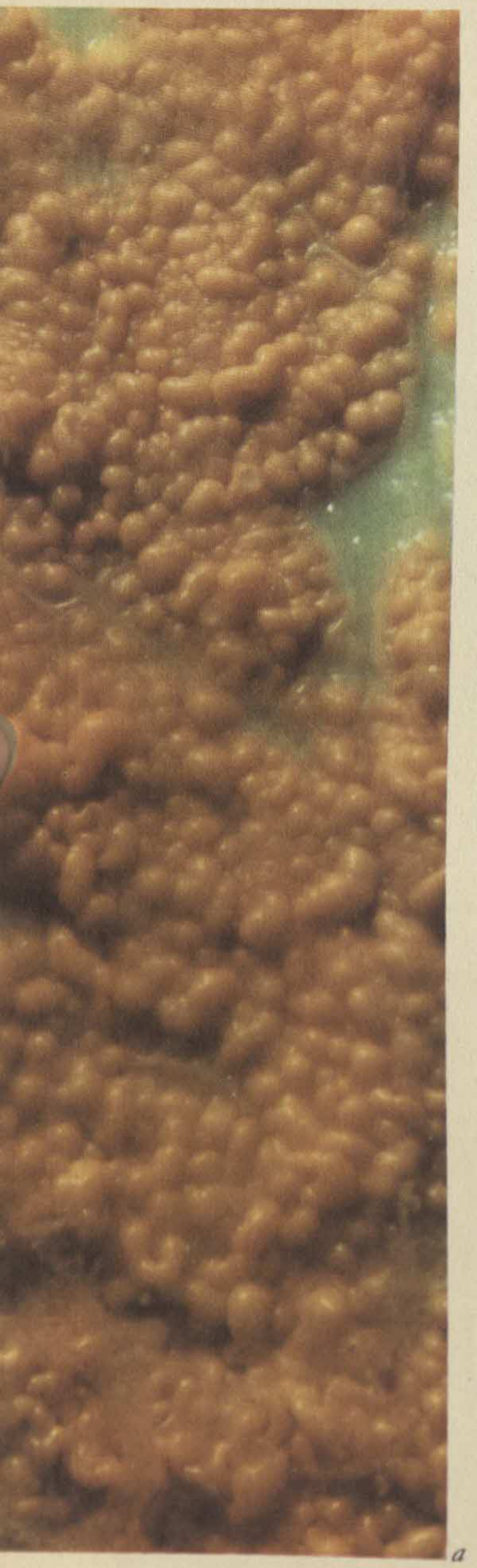
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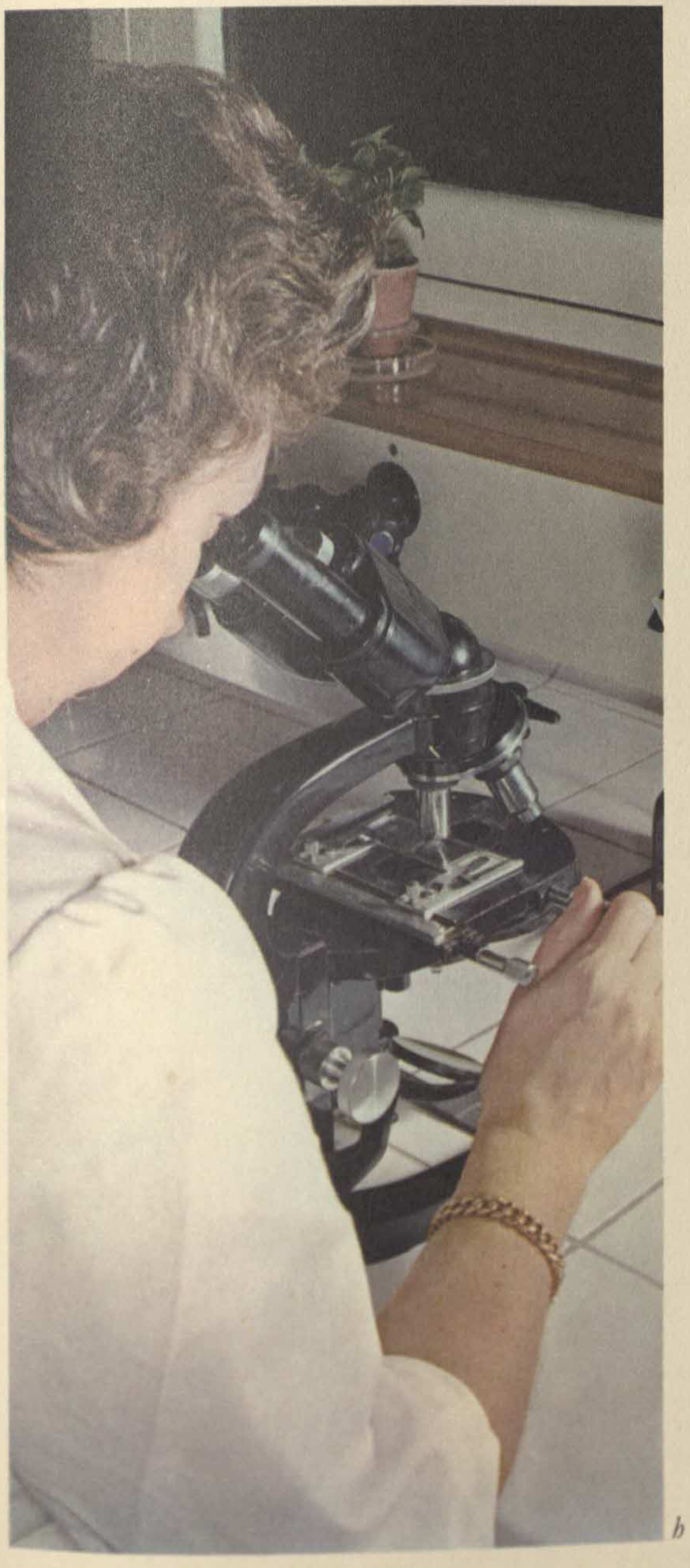
at Garches, except photograph A, which comes from the laboratory of Professor J. G. Marchal, of Nancy University, and photograph P, which was taken at the Hôpital Saint-Antoine in Professor Kourilsky's department. Photos Lod).



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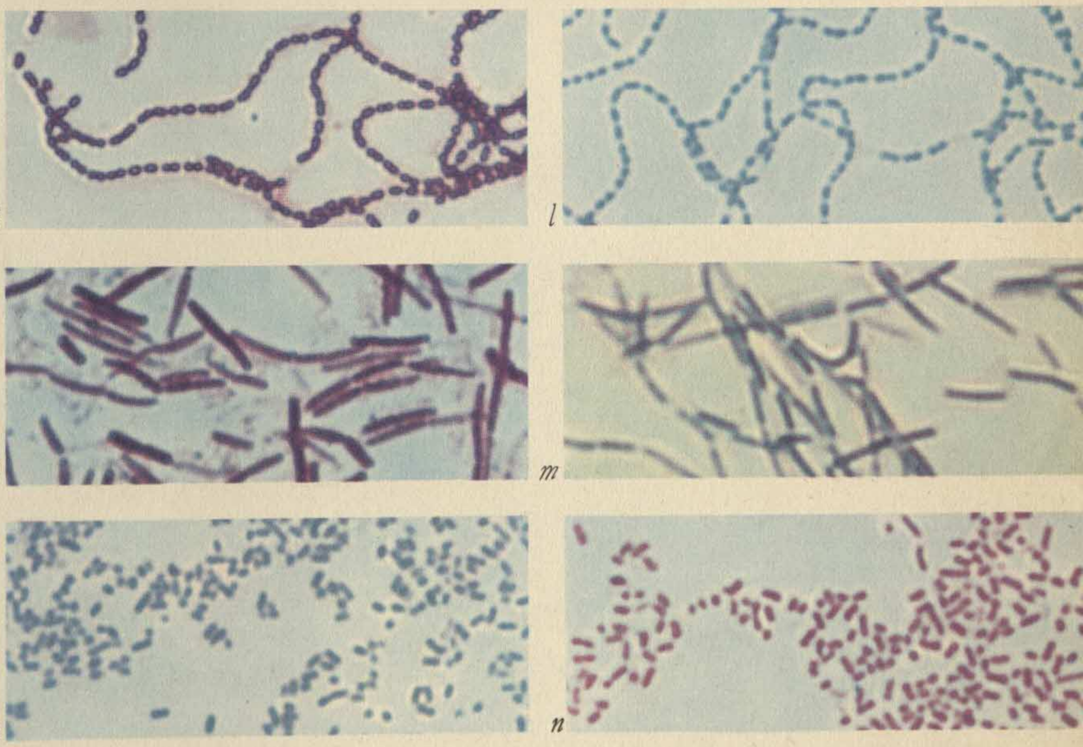
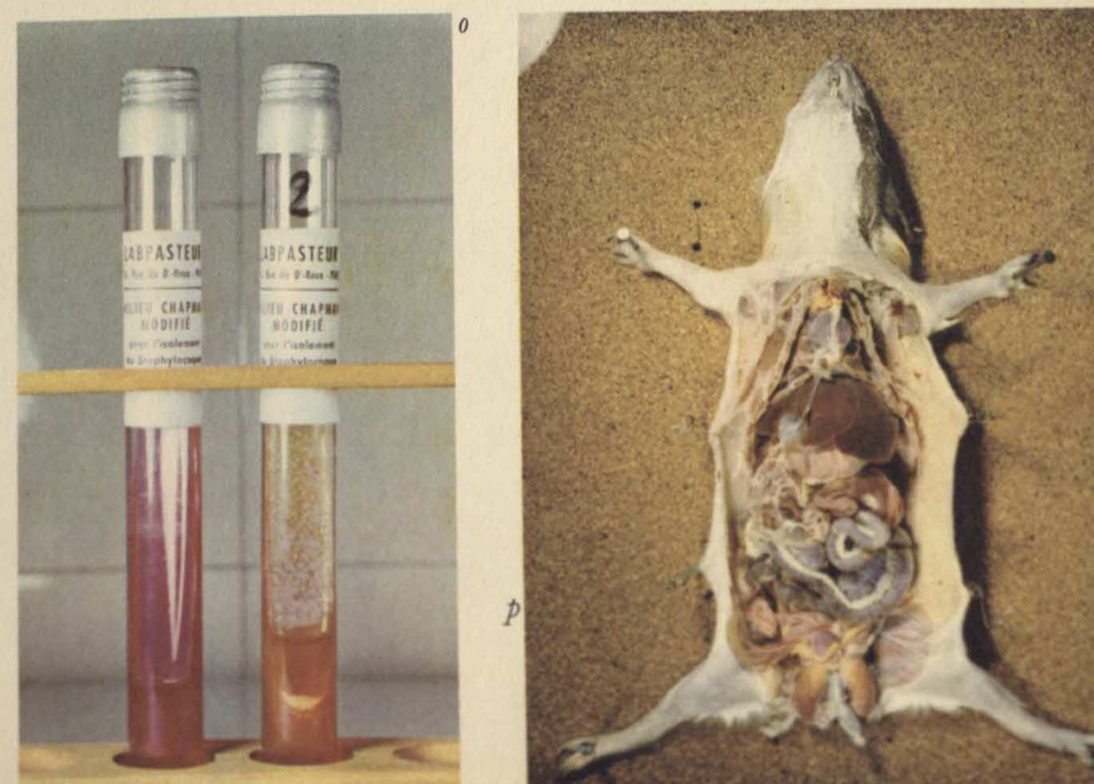


Some types of bacterial culture: i. Anthrax bacteria, double Gram stain (Gram$^+$); chains of cocci, coloured violet on a clear background (mag. × 1,230). j. Anthrax bacteria, double Gram stain (Gram$^+$) thick violet rods (mag. × 1,230). k. Colibacilli, methylene blue stain, blue on clear background (mag. × 1,230). l. Streptococci, methylene blue stain, cocci in chains, blue on clear background (mag. × 1,230). m. Anthrax bacteria, methylene blue stain, thick blue rods (mag. × 1,230). n. Colibacilli, double Gram stain (Gram$^+$), pink bacilli (mag. × 1,230). o. Chapman's medium; differentiation between pathogenic or saprophytic staphylococcus: 1. saprophytic, colour unchanged, small pink colonies; 2. pathogenic, colour changed to yellow, numerous colonies. p. Dissection of previously inoculated laboratory animal.



One of the first pathogenic germs to be identified: the anthrax bacillus. Besides a normal form, another is seen in the course of lysis. (Mag. × 38,000; microphotograph by F. Scanga, Istituto Superiore di Sanità, Rome).

nervous system (caused by the poliomyelitis virus or the syphilis bacillus) carries a strong risk of its being followed by paralysis. Tetanus is always characterized by muscular rigidity.

These easily understood functional symptoms are nearly always accompanied by symptoms which are truly characteristic of a particular disease. Thus eruptive illnesses are all denoted by cutaneous marks, although the manner in which each eruption arises, develops, and ends is not so obvious. No doctor, confronted with a patient who has an eruption of a manifestly infectious nature, would hesitate long in diagnosing typhoid fever, measles, scarlet fever, or smallpox. In his diagnosis he will take account of the way in which the cutaneous marks arose, their appearance, number, and development. This last word—development—should be emphasized, since the characteristic cycle of the chief infections must be known. In the development of typhoid or scarlet fever, to take these two from among many examples, it is, in fact, easy to distinguish an incubation phase, an invasion phase, a localization phase, and, finally, a terminal period marking either recovery or death.

It is generally reckoned that the *incubation phase* tallies with an invisible process of local multiplication together with dissemination of germs within their host. This phase may be very short or very long (one to fifteen days for poliomyelitis, one to two weeks for smallpox and epidemic typhus, two weeks for typhoid fever, ten days for measles, forty days for rabies). The main symptom during the *invasion phase* is a rise in temperature which may take place very quickly or very slowly. For example, in lobar pneumonia there is a quickly-rising temperature. A slowly-rising temperature, on the other hand, is the rule in typhoid fever. The *overt phase* is variable in its duration from one case to another and can last for days or weeks. Even when the temperature returns to normal, it cannot be said that all danger is past. Relapses may occur (frequent during the development of typhoid, and even more so in cases of rock-fever). It is also during the overt period that complications can occur. The main infectious diseases that assail man all carry with them the danger of certain complications. In typhoid fever, intestinal complications are to be feared (haemorrhage and perforation). In measles, broncho-pneumonia can occur. In scarlet fever, the risk of nephritis predominates, and so on. Today, we are still badly informed on the exact pathogenicity of these different complications. Germs of a secondary infection are often involved. The first infecting bacteria or viruses may have 'awakened' germs in the organism under attack, germs which up till then have gone unnoticed because they were dormant.

It may happen that an illness, once the acute phase has been passed, ends neither in recovery nor death, but lingers on in an intermediate stage and becomes chronic. Tuberculosis is an excellent example of this.

The enigma of infectious diseases

A great deal of progress has been made during the last century in our knowledge of pathogenic germs and the infectious diseases they cause. We have been able to identify nearly all these germs (bacteria, viruses and parasites) and the development of each illness has been carefully studied. We now know what is most to be feared and therefore what first needs to be looked after. Remarkable and surprising progress has also been made in anti-infectious treatment in the last few decades. We must recognize, however, that many factors in the pathology of infection still remain unknown. The first of these factors is that a person in apparently good health is comparatively often found by chance to be harbouring a pathogenic organism, diphtheria bacillus, typhus bacillus, and so on. Such persons are called germ-carriers and must be regarded as dangerous to those around them. How is it that they can carry these germs with impunity? What mechanism protects them? The idea of the intervention of phagocytes or antibodies is not convincing. There is probably some other fundamental reason. In searching for this, one becomes aware that the healthy carrier acquires serological properties, particular cellular properties that prevent the pathogenic germs from multiplying and producing their toxins.

On the other hand, cases are known where an *explosive infection* occurs, and nothing appears to be any longer capable of arresting the spread of bacteria. Staphylococcus, for example, enters unobtrusively through a small skin wound. There is nothing to indicate that it is to be feared; nevertheless, on arriving at the connective tissue, it suddenly begins to reproduce. It thrusts aside the white cells, the macrophages, that come to destroy it. It enters the lymph channels; after it is in the blood, it explodes into a septicaemia. Secondary localizations are produced here and there, but no antibiotic will be of any use. The patient, at first hyperthermic, becomes hypothermic, falls into a coma, and dies. Why is this sequence of events so inexorable? The whole problem of bacterial virulence is at issue. A great number of factors must intervene, notably the rapid destruction of phagocytes by bacterial enzymes. Once dead, the phagocytes supply the bacteria with an excellent culture medium.

There is another unknown factor in the picture of infectious diseases: why, after dissemination through the whole body, does a germ, bacterium or virus, tend to become localized? Each germ, as we have already suggested, seems to have an affinity for a particular organ, but the whole phenomenon remains unexplained. In the same way, the cyclical nature of the development of the great infectious diseases often remains obscure, although in some cases (malaria, pneumonia), the phenomenon has been, on the whole, satisfactorily explained.

A fresh subject for consideration is that of healing. Certainly, in the simplest cases (a whitlow or a tooth abscess) it is easy to guess how healing comes about; phagocytes have intervened and destroyed the micro-organisms. But is it possible to speak of phagocyte intervention to explain the cure of the great cyclical diseases and viral infections? It is not certain. An antibody action might be a possibility, although some patients can recover apparently without having made antibodies. It is also a possibility that interferon, discussed in the fourth volume of this work,[2] has made an appearance. Certainly, there are numerous processes open to the organism.

There is one further step to be considered. An infection leaves behind a certain state of immunity, which may differ remarkably from one case to another. Sometimes the immunity may be regarded as definitive, as for example in typhoid fever, cholera, plague, measles, chicken pox, mumps, smallpox, epidemic typhus, poliomyelitis, and yellow fever. Immunity is very transient, however, in the case of herpes, colds, and influenza. To what may this difference be attributed? Here the idea of antibodies, although so important, is not of much use to the biologist. It would be better to speak of a special modification of the cell-parasite relationship.

Finally, we must ask why certain diseases (tuberculosis, vaccinia, and syphilis) leave the body in an unusual state characterized by an accrued sensitivity to the toxins of the specific germ. This is currently known as *allergy*. It is thought today that the origin of this state is due to antibodies or, more precisely, to antibodies linked to cells. The reader will find more information on this matter in the chapter on 'Anaphylaxis and Allergy' in Volume 4.

The pathology of infection, as we see it today, is of the highest importance. Moreover, there is nothing to dispel the thought that diseases due to microbes at present unknown may appear in the future. Everyone has heard of the theory, so well expounded before the war by Charles Nicolle, about the birth, life and death of infectious diseases. We should, however, be thankful for the amount of protection which the progress of science has already given us and remember the great epidemics of history, about which we can learn only from books. Although the microbiologist and the doctor have not yet completed their work in this field, a great deal has been done. Through their work, as Pasteur said in a famous speech, they have replaced jungle rule by the rule of humanity.

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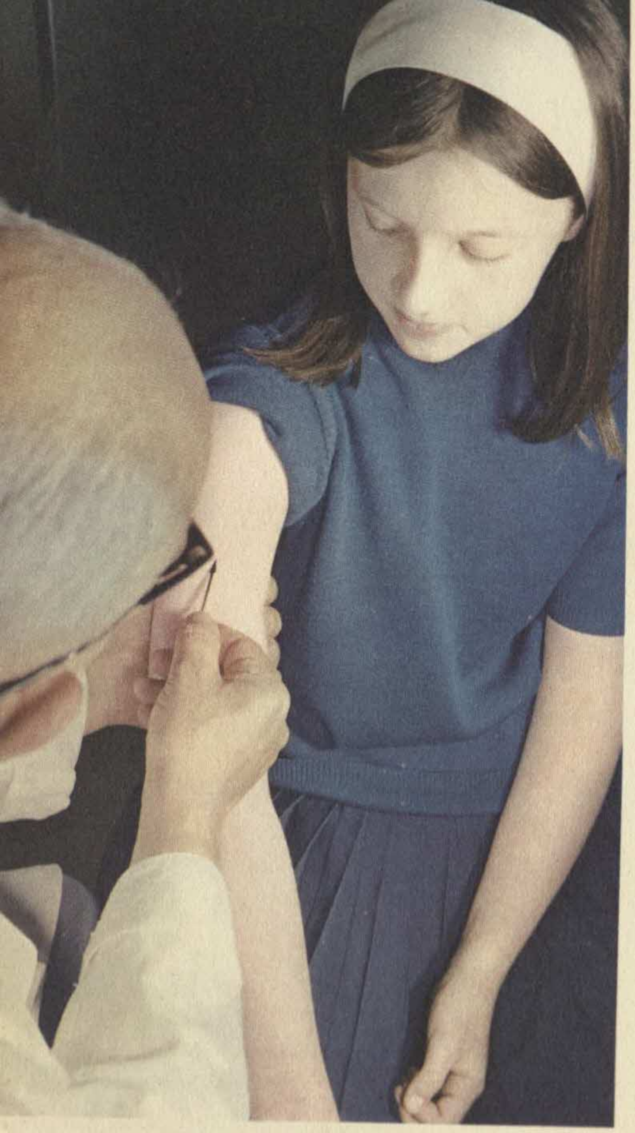
(2) *See the chapter on interferon by Dr Alick Isaacs in the volume entitled 'The World of Microbes'.*



A skin-reaction test is carried out by the doctor in order to detect primary tuberculosis.

Forms of tuberculosis

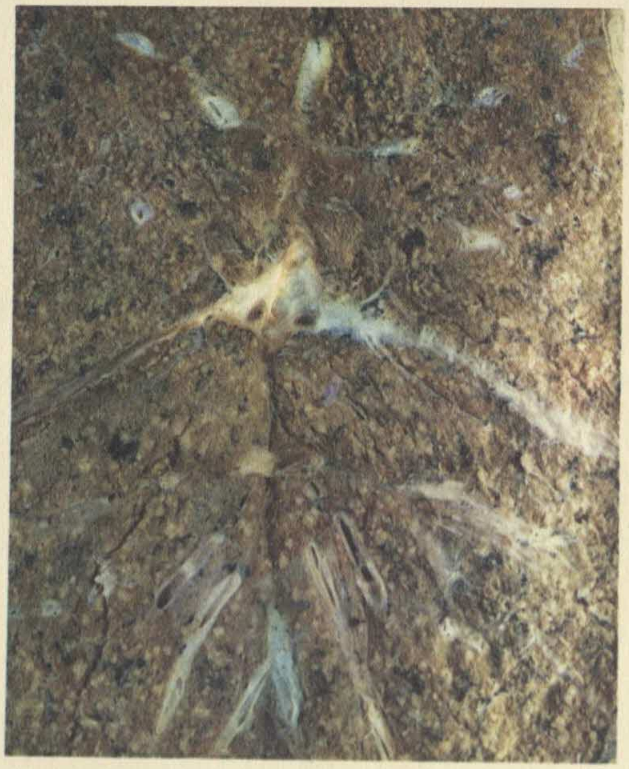


Fig. 1. Acute miliary tuberculosis: small lesions, scattered like millet seeds, are just visible.

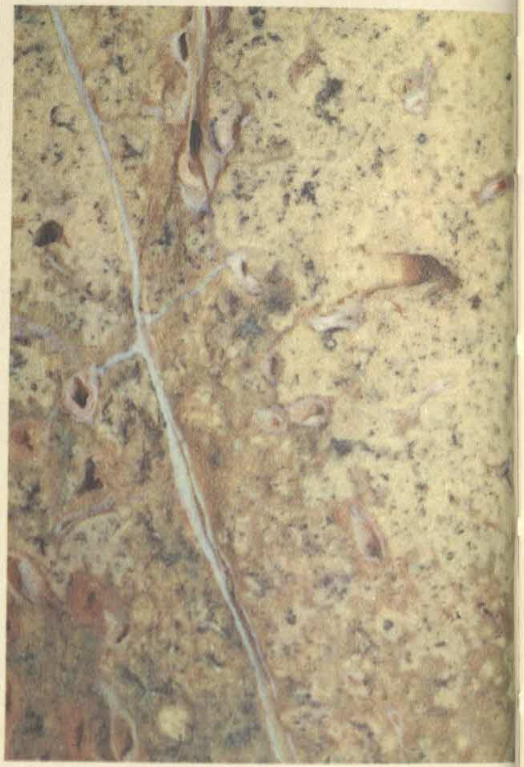


Fig. 2. Acute pulmonary tuberculosis: on the left can be seen the confluence of foci of caseous necrosis.

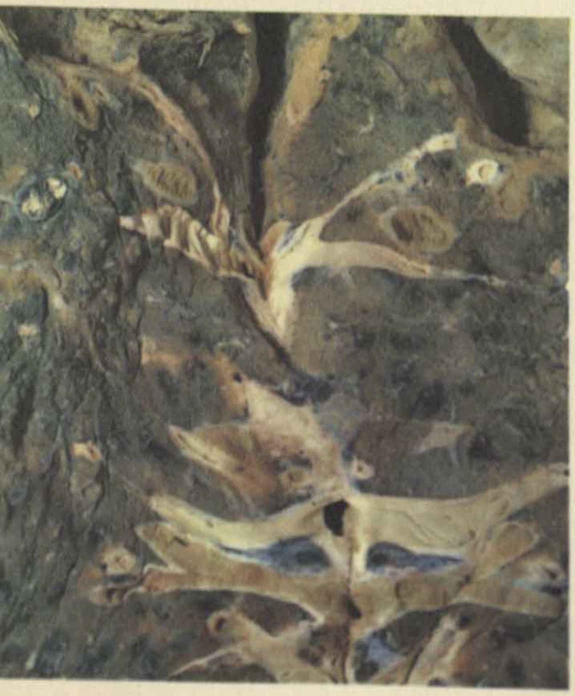


Fig. 4. Confluent lobular tuberculosis: on the left and above are several lymph nodes of increased volume.

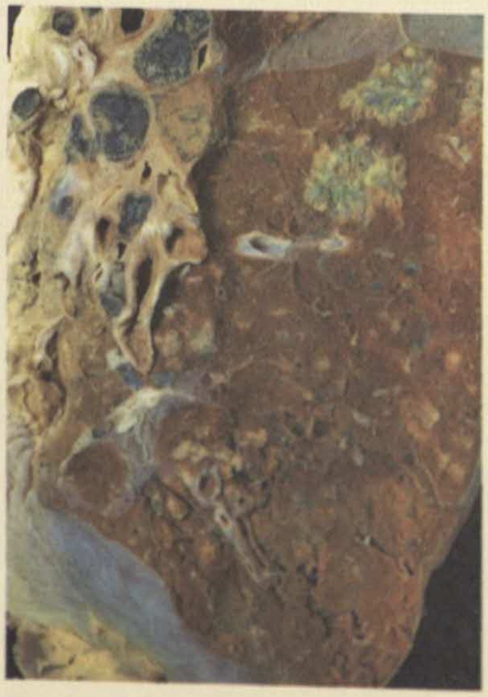


Fig. 5. Diffuse chronic pulmonary tuberculosis with scattered tuberculous lobules.

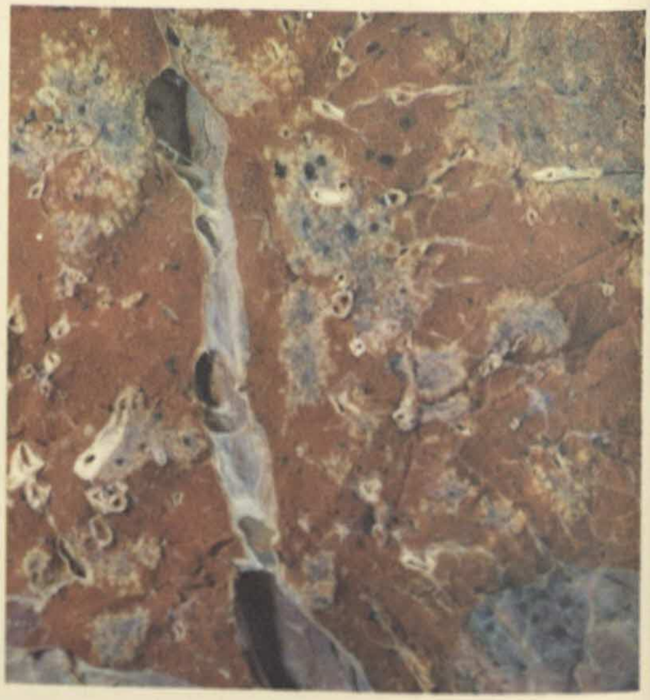


Fig. 6. Broncho-pulmonary tuberculosis: note the presence of dense scar tissue in the middle of the photograph.

Tuberculosis is undoubtedly the most widely-known bacterial disease, but in speaking of it we usually mean lung tuberculosis, although many other other localizations are possible. The photographs on the left show different aspects of lung tuberculosis; those on the right show some visceral tuberculoses. (From Professor Kourilsky's personal museum of clinical medicine, Hôpital Saint-Antoine, Paris. Photos Lod).

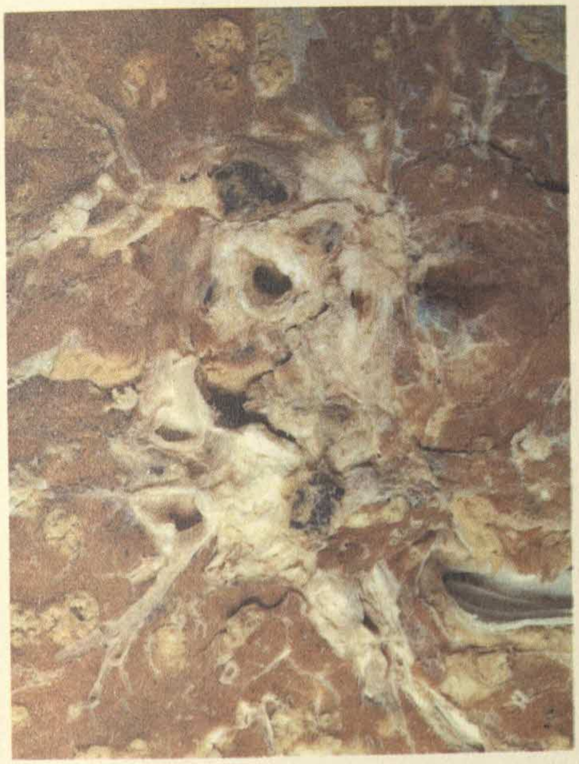
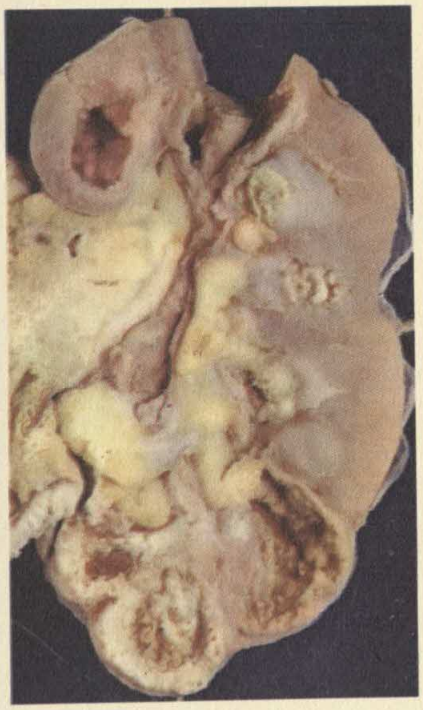
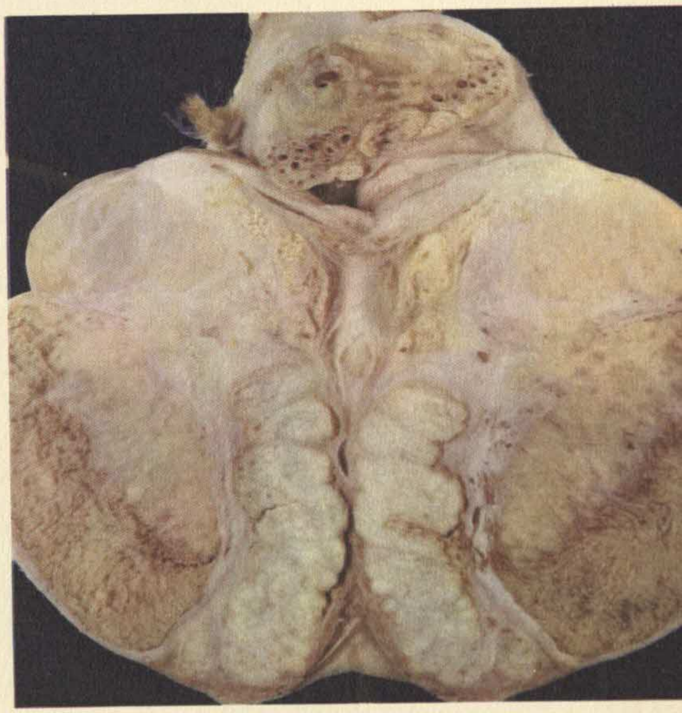


Fig. 3. Localized tuberculosis: at the top there is a cavity resulting from the elimination of necrotic tissue.



Renal tuberculosis, cavity type.



Genital tuberculosis, testis.

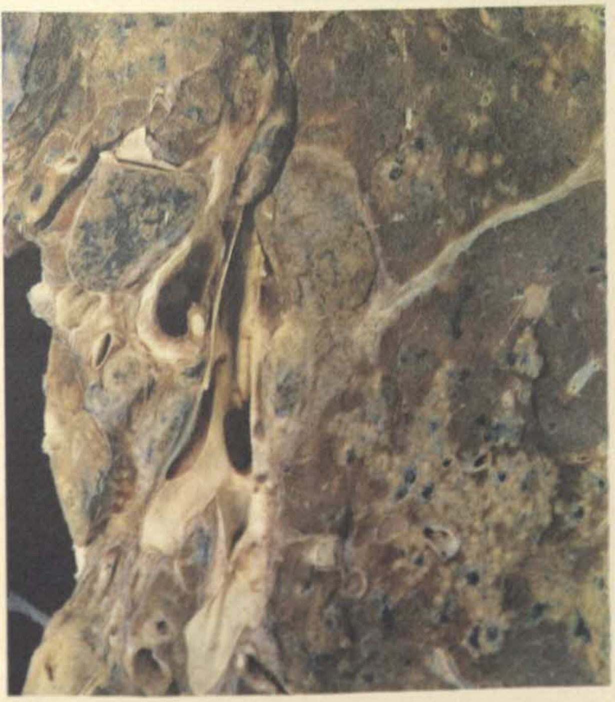
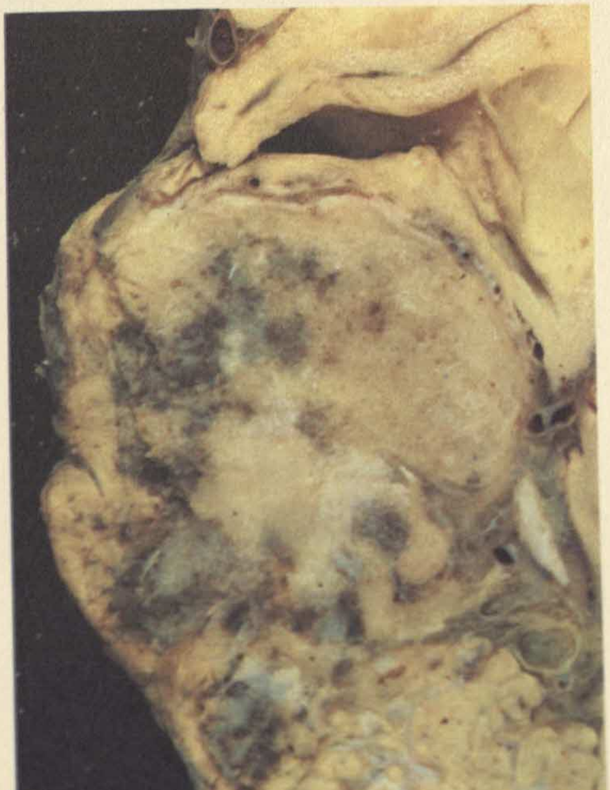
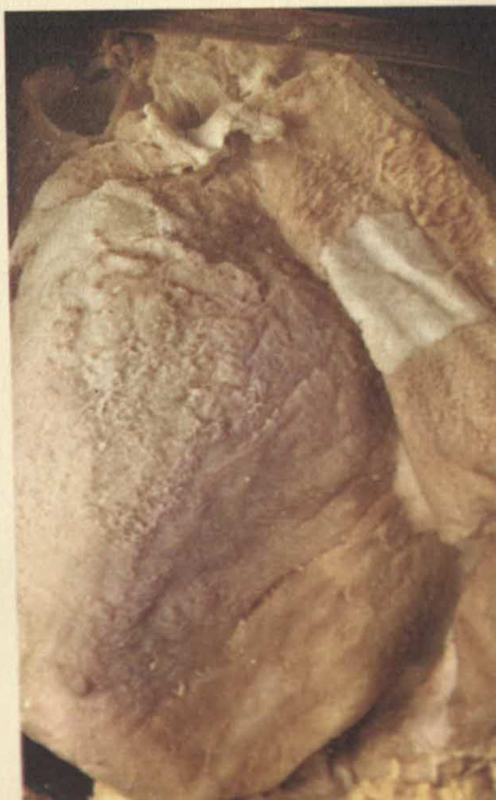


Fig. 7. Diffuse tuberculosis with lobulites (the term lobulites corresponds to a lobular lesion).

Renal tuberculosis, detail.



Tuberculosis of the pericardium.



Tuberculosis

Fernand CARDIS

Tuberculosis is a disease that has nearly been conquered. Can it be finally overcome? Certainly, an enormous amount of ground has already been covered, and antibiotics have proved to be marvellously successful in curing the disease, but the efficacy of antibiotics in prevention is not wholly known and in no way can they replace B.C.G. vaccination.

In medicine there are few examples of a quicker or more successful, fight against a social scourge than that carried on against tuberculosis during the last twenty years. True, this struggle had been achieving results since the beginning of the century. From the curve of tuberculosis mortality, it is possible to trace the rise in the number of out-patient clinics, of their efforts to detect the disease, of the gradual establishment of sanatoria, and of the spread of collapse therapy methods.[1]

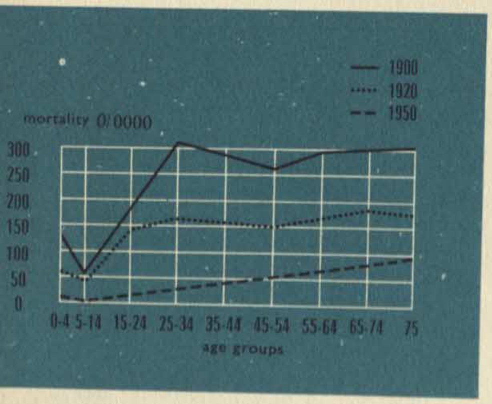


Fig. 1. Tuberculosis mortality figures in the United States, in relation to age, expressed in $^0/_{0000}$ *(taken from Woodruff).*

Epidemiology

In 1900, the mortality rate from tuberculosis was approximately between 25 and 30 $^0/_{000}$; in 1948 it had fallen to 5-7 $^0/_{000}$. The discovery of anti-tuberculosis drugs—an antibiotic, streptomycin (SM) in 1947, and two chemical agents, para-aminosalicylic acid (PAS) in 1948 and isoniazid (INH) in 1951—has altered the mortality curve in a startling manner; in 1960, deaths from tuberculosis had sunk to about 1 $^0/_{000}$ and even lower (in Holland, Denmark, and the United States). For the first time, we possessed a weapon for direct attack on the germ of the disease, Koch's bacillus *(Mycobacterium tuberculosis)*. It was a weapon which demonstrated the superiority of aetiological therapy over symptom treatment. Up till then one had to be content simply to reinforce the natural defences of the organism and to provide symptom treatment.

One other demographic aspect will help us to realize what an immense amount has been accomplished: the study of the relative tuberculosis mortality rate, which defines the share of tuberculosis among all the causes of death. At the beginning of the twentieth century it was about 25 to 30 per cent, while today it is not more than 0·1 or 0·2 per cent.

It is interesting to examine these two concepts of the tuberculosis mortality rate and the relative tuberculosis mortality rate for the age groups of those who succumb to the disease. Here the change is equally startling. In the United States, Woodruff described the situation in 1900, 1920 and 1950. The curve has completely altered in shape; in 1900 it was uneven, climbing from 15 $^0/_{000}$ in babies up to 30 $^0/_{000}$ at twenty-five years, after a fall to 5 $^0/_{000}$ at five years, and it sank to 25 $^0/_{000}$ at forty-five years, only to rise to 28 $^0/_{000}$ at seventy-five years. In 1950, it dropped to 00·3 $^0/_{000}$ for babies and to 0·15 $^0/_{000}$ for five-year-olds and from there showed a slow linear ascent up to 5 $^0/_{000}$ at seventy-five years. This shows us that:

1. While the peak of the curve has been displaced towards the right, ie, towards old age, the mortality rate for all ages is considerably lower;

2. The greatest benefit concerns babies, then young people and adolescents up to the age of twenty-five. Thus the average age for death from tuberculosis keeps going up. This applies both to the disease itself and to the probability of infection by the tubercle bacillus, which we shall explain later.[2]

If we set aside mortality from tuberculosis and study only the statistics relevant to the disease itself, we find that the figures are only approximate. It has been known for a long time that for every death from tuberculosis there are five persons with the disease. Surveys seeking to establish such a proportion have shown that, in Switzerland at least, in 1945 in the canton of Zurich, and in 1959 in the canton of Vaud, the proportion was considerably higher—as much as 15 or 20 to 1. However, this figure is dependent on a specific definition of the disease, always a difficult concept to define.

Tuberculosis does not behave like other

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(1) *Collapse therapy methods consist in partially immobilizing the patient and in reducing the volume of the affected lung, usually by artificial pneumothorax or thoracoplasty.*

diseases. It may implant itself in the organism without harming health (latent tubercular infection), or it may cause immediate illness (patent tubercular infection). Between these two extremes are many variations in development, including serious and even advanced damage in a person who is unaware of it (this is known as hidden tuberculosis). Latent infection is found in people who have once been contaminated with the Koch bacillus and are tubercular without suffering any harmful effects. A positive tuberculin reaction in the absence of apparent illness is the only revealing sign of the presence of the disease. However, radiological evidence of a first lesion is sometimes to be observed, indicating a primary infection. Latent infection can become patent either through multiplication of bacilli found in the primary scars which temporarily enclose them, or through over-infection by external bacilli through the agency of fresh contamination.

The transformation from one form to another is often insidious and undetected, so much so that a random radiological investigation can reveal signs of tubercular activity where there are no symptoms to show the least indication of it. The dividing line between health and sickness is hard to trace; doctors are often confronted with this problem. In fact, the existence of hidden tuberculosis and the danger it represents for the carrier and those around him have led to the use of many diagnostic methods; the most widely used is that of mass X-ray screening of healthy people. The value of this method is inestimable and has to a large extent contributed to the success of our efforts. X-rays can detect even extremely slight patches, generally at the apex of the lung at a pre-clinical stage when it is possible, at little cost, to apply therapy that will be rapidly and completely efficacious.[3]

However, everything that contributes towards weakening the prevalence of the disease plays its part: systematic mass examinations make it possible to effect early and completely successful treatment; the isolation of carriers and subsequent protection of society; the drugs themselves, which today can quickly sterilize sputum and diminish contagion; and the prevention by use of the B.C.G. vaccination. Thus, medication is not the only weapon and we must not neglect the other means. However, our methods of treatment, even if they save numerous people from death, do not always cure them; it is known (Milliet) that the number of those stricken by tuberculosis in Belgium trebled between 1948 and 1957.

Therapy

The *first stage*, of which we have already spoken, is that of primary infection, or installation of the bacillus in the organism. We know today (as much by means of tagged bacilli in experimental infection of laboratory animals as by tagged B.C.G. injections in man) that Koch bacilli spread extremely rapidly through the organism during the days following infection during incubation, even before the appearance of the primary complex. It is not usually known exactly when infection occurs. However, from the moment primary infection is identified, either on a lung radiograph or from the change in the tuberculin-reaction test, treatment must be begun at once. This treatment should, in our opinion, be given to all age groups, but it is essential for babies. In these cases, INH[4] and PAS[5] should be given, and in serious cases, streptomycin. There is no point in laying down a general scheme for their use, since this varies with each individual case. For cases of primary infection without symptoms, detected in later childhood and afterwards, a treatment is to be applied which is incorrectly called 'chemoprophylaxis'. What it means in fact is the neutralization of the spread of bacilli and the avoidance of subsequent trouble. Here again, a combination of INH and PAS is advocated, administered over a period of at least six months.

The combination of two or more antitubercular drugs is necessary because of the existence of strains which are resistant to a particular drug and which would multiply if such a drug were administered alone; bacilli resistant to one preparation do, in the immense majority of cases, respond to another.

The secondary stage is that in which localizations of the disease appear in different parts of the body, in the pleura, meninges, peritoneum, bones and joints, urogenital system, eyes, skin, etc. The great innovation concerns essentially the treatment of tuberculous granulation—which until recently caused death within a few weeks by a dispersion of generalized tubercles throughout the body—and in treatment of meningitis and pleurisy. In these three forms the disease is mastered nowadays by the use of SM, INH and PAS, provided that energetic action has been taken early (in the first week). Cortisone derivatives have been extremely useful additions to specific medication. For example, meningitis, which was fatal in the past, is now cured nine times out of ten.

(2) *This change in the average age is unquestionably due to the increasing scarcity of sources of contamination, according to the formula* ts = *a constant, where* t *stands for the time required for contamination and* s *is the density of contaminating sources; this means that the average age for tuberculous infection rises as the number of sufferers with infected sputum falls. The proportion of tubercular mortality between twenty and forty years of age was approximately 70 per cent in 1900; in 1948 it was 30 per cent, and in 1953 20 per cent. There is a curious and profound change in tubercular mortality according to sex. Up to about 1940, female mortality in Switzerland was higher than that of males; but since then the ratio has been reversed and male mortality becomes higher and higher.*

(3) *Total illness (or prevalence), that is, the total of persons treated or supervized for tuberculosis in Western Europe, is at least* $15\ ^{0}/_{000}$. *But, to appreciate the real spread of endemic tuberculosis, we must take into account new cases detected during the year; that is, the annual incidence of tuberculosis. This is slowly falling, despite the now relatively high number of 'minor cases' with slight radiographic images. But its power to kill those it attacks*

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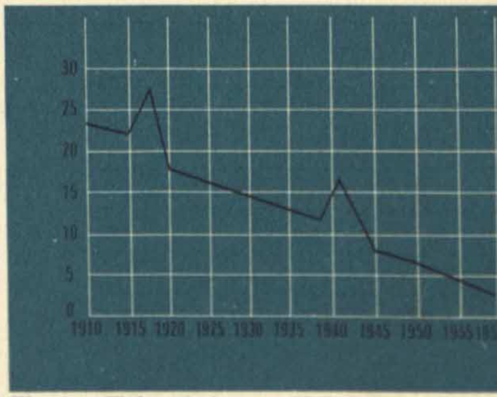

Fig. 2. Tuberculosis mortality per 10,000 inhabitants in France. Note the recrudescence of mortality during the two World Wars.

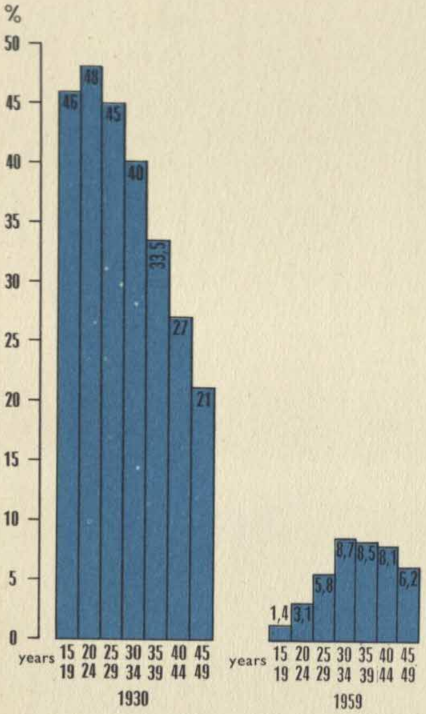

Fig. 3. Relative tuberculosis mortality rates in France in 1930 and 1959 for the two sexes.

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has considerably diminished. It is difficult, however, to estimate the real effects of this power. One has to consider the ratio of deaths to the number of persons who have tuberculosis but do not die from it.

Mortality varies considerably according to age. In infants, tubercular infection is always an illness and is always serious; in 1952, mortality for those aged less than six months was still 25 $^0/_{000}$ (Fouquet); in 1956, it fell to 2 $^0/_{000}$; before the advent of chemotherapy it was 60 $^0/_{000}$. The age of least danger from contamination is between five and fourteen years of age. The most powerful factor in the reduction of tuberculosis mortality is the introduction of antibiotics.

As regards the *tertiary stage*, or pulmonary tuberculosis, treatment takes three forms: treatment in a sanatorium, treatment at home, and ambulatory treatment.

Today, as in the past, patients who are spreading Koch bacilli or who are affected by extended lung cavities or lesions should be in sanatoria. They are made to rest, and it is in such sanatoria that they will receive the best and most rapid benefits from combined antibiotic and chemotherapy. In sanatoria, they will find the best and most suitable psychological atmosphere; treatment today is based as much on future readaptation for work and re-entry into society as on cure. Many antibiotics and chemicals have been found to back up the 'famous trio', of which streptomycin and INH at least are unsurpassed —ethionamide is clearly more active than PAS, but is less well tolerated. New treatment has superseded artificial pneumothorax, which is now rarely employed. When recovery is slow, the new surgical technique of pulmonary excision is adopted. This consists of removing part of a lung (segmentectomy and lobectomy) or even the whole lung (pneumonectomy). Such methods are satisfactory in that they remove dead areas, but the pulmonary system suffers because some healthy tissue is always lost. Thoracoplasty, which resects the ribs where the lungs have been attacked. is still a technique not fully documented. At present, the substitution of pneumothorax by anti-tubercular drugs has proved advantageous, since bacteriostasis does not entail complications due to lung collapse. However, only time will tell whether or not a step forward has been achieved, because the real danger here is of relapse, and this danger may still exist for anything up to ten years afterwards.

Owing to chemotherapy, the length of sanatorium treatment has been considerably reduced; in fact, administration of anti-tubercular drugs can, and should, as a general rule, be carried out at home for as long as is thought to be required.

Treatment at home should be the same as that carried out in a sanatorium, but this is a makeshift arrangement and should be adopted only if entry into a sanatorium is impracticable (as in the case of babies, young children, old people, and those who are mentally un-adaptable) and provided that adequate measures are taken with regard to the sick person and those around him.

Ambulatory treatment is both economically and psychologically advantageous: there are no sanatorium expenses and no loss of income is to be feared, since the patient is able to continue working; nor does he suffer the shock of being suddenly cut off from his social environment and no readaptation problem is involved. However, this treatment is appropriate only to slight forms, where the patient does not spread tubercle bacilli (established by means of extensive sputum tests, or failing these, by means of stomach-tube tests). If these rules were not strictly adhered to, we would run the risk of perpetuating tuberculosis in the community. As in the case of chemoprophylaxis, at least two combined drugs are administered: INH and PAS (or possibly INH and ethionamide) in sufficient doses and for an adequate period of time (twelve to eighteen months or more).

Prophylaxis

One last word on prophylaxis (chemo-prevention, according to R. Debré). Some research workers (Omodei, Zorini) advocate the use of chemical substances. In this case, INH is distributed to those who are exposed to contagion but who have not yet contracted tuberculosis. However, this method is inconvenient because the drug has to be given indefinitely and we believe that it will be difficult to make it really acceptable. The best and surest prophylaxis is probably still B.C.G. vaccination. For babies, the oral route at the dosage suggested by Etienne Bernard seems the best; for adults, the scarification method (Bretey) or intradermic application (Wallgren) is preferable. More than 100 million people all over the world have been vaccinated with B.C.G. and the most varied statistics show that, among these people, death from tuberculosis is six to ten times less than in those of the same age who have not been vaccinated and who live in similar conditions.

What conclusions can be drawn from this rapid survey? The different weapons in the fight against tuberculosis; detection carried out by means of repeated X-rays of whole populations, especially adults and old people; systematic searches for tuberculous infection by means of tuberculin tests; early and thorough treatment of sick people; isolation in a sanatorium for those who are spreading tubercle bacilli; and B.C.G. vaccination—all these factors, if carefully co-ordinated and widely used, enable us to glimpse a solution to the problem of tuberculosis. The gains achieved to date can only serve to encourage us to pursue our task unceasingly until the disease has finally been eradicated.

(4) *Isonicotinic acid hydrazide (isoniazid) 15 mg per kg bodyweight per day.*

(5) *Para-aminosalicylic acid (15 g per day orally or intravenously).*

Influenza

J. MULDER

What is influenza? Many people give this name to winter or spring infections and to different sorts of fever. Yet the nature of influenza is clearly defined. The causal virus has been identified with strict precision and cultured; it is quite different from the numerous viruses continually being discovered as the causes of other seasonal infections. This chapter outlines the essential characteristics of this illness, which is liable to serious epidemic outbursts.

Influenza is an acute contagious illness caused by a virus which attacks the ciliary epithelial cells lining the respiratory passages, ie, the inner walls of the nose, trachea, and bronchi. The word *influenza,* coined by the Italians in the middle of the sixteenth century (and adopted by the English) is derived from what at that time was believed to be the 'influence' of cold. Plague, smallpox, and cholera have now been mastered and appear only in the form of localized epidemics; but two or three times in a century, influenza still takes on a generalized pandemic aspect. This affliction breaks out on a world-wide scale, always with a very high death rate.

The influenza virus is a very small microorganism with a diameter of 1/10,000 of a millimetre which develops exclusively at the expense of the cells of the human body. The action of different viruses on different types of cells is specific; in other words, particular cells favour the development of particular viruses. When the ciliary epithelial cells are infected by the influenza virus, they die and are destroyed. Superficial microscopic excoriations of the respiratory passages appear. People who are infected spread the virus among others by sneezing and coughing.

The discovery of the influenza virus

The history of the very important discovery of this virus is interesting. Before 1933, the causes of influenza were completely unknown and no animal had been found which could contract the disease by contagion. It was then observed at the National Institute for Medical Research in London that the water from mouth-washes of infected people could infect the ferret. This animal had been chosen because it is strongly susceptible to distemper, another virus disease. The first announcement of the transmission of human influenza to the ferret was made by Dr W. Smith, Dr C. H. Andrews and Dr P. P. Laidlaw. Soon after this discovery, it was observed that the modified virus could be passed from the ferret to the mouse. From that time, experimental material was available which opened the way for extended research. In 1935, Sir M. Burnet showed at the Walter and Elisa Hall Institute for Medical Research in Melbourne that the virus also developed in the chick embryo, attacking not only the lungs but also the superficial cells of various external membranes.

The next stage, a great technical advance, was reached when in 1941, Dr K. Hirst of the Rockefeller Institute for Medical Research in New York, discovered that the virus could attach itself to the red cells of the blood; these agglutinate and form small clumps when the virus is present. This simple technique, still in use today, enables small laboratories to pursue large-scale research relating to the

Fig. 1. The ferret is a small animal used by scientists for experimental work, especially for research concerning virus studies on influenza. (Photo Lod).

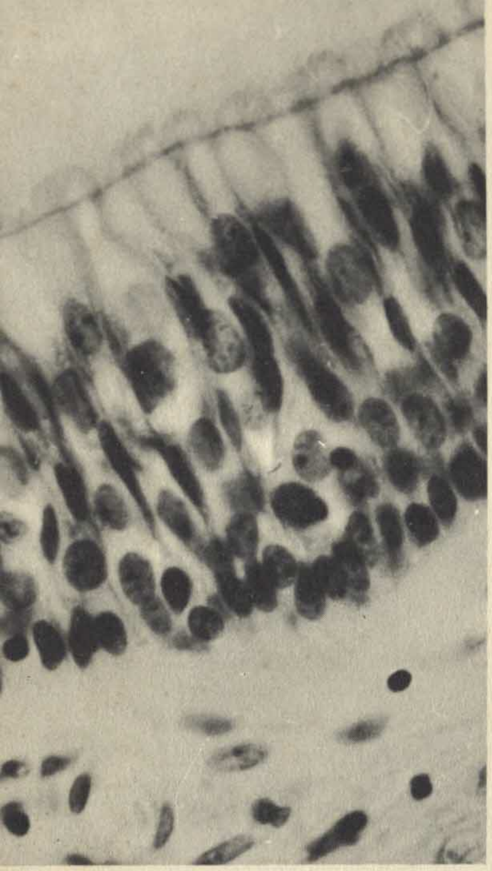

Fig. 2. Lining of the tracheal mucosa in man. This lining is composed of elongated cells the surface of which is covered with cilia. (Mag. × 1,200).

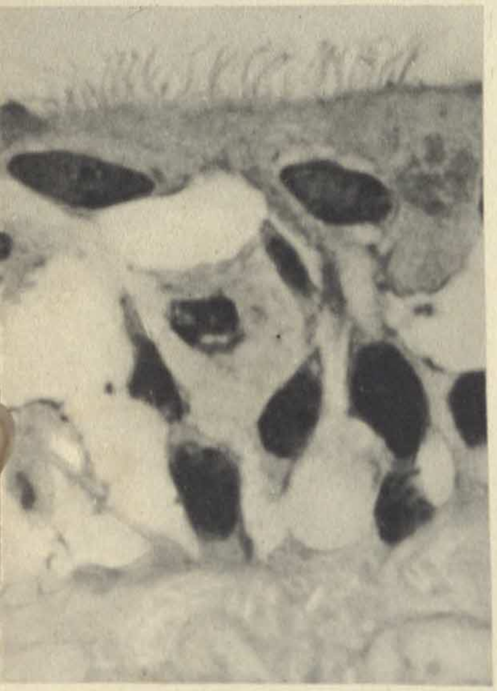

Fig. 3. Ciliated cells infected by influenza virus. Cells that have lost some of their cilia are retracted: vacuoles are formed in the intercellular spaces. (Mag. × 2,000).

problem of influenza. It is remarkable that in such a short space of time, the virological diagnosis of this mysterious affliction should have become so easy to establish and as certain as bacteriological diagnosis of, for instance, typhoid or septicaemia.

Laboratory diagnosis by use of the egg-inoculation method takes two or three days, though for some years now it has been possible to perform the operation even more quickly by using a process called the fluorescence method. This was developed by the Americans Coons and Kaplan in 1950. Its principle consists in associating the material containing the virus with a specific antibody present in the serum of convalescents or experimental animals (ferrets). If this antibody has previously been treated with a fluorescent substance (fluorescein), the virus-antibody complex is visible in the fluorescence microscope, where it appears coloured yellow.

Using this technique with nasal mucosa or the sputum of patients, ciliary cells attacked by the virus appear within a few hours as brightly coloured yellow bodies. This method, however, can only be carried out in specially equipped laboratories.

Clinical development of the disease

Generally speaking, influenza is not dangerous. The temperature, which may reach 40°C or 41°C, subsides in two or three days, sometimes rising again to a new peak on the fourth or fifth day (fig. 1). The main symptoms are a slight rhinitis, cough, headache, insomnia and general muscle-ache. In many cases, the patient's temperature is not very high and the illness does not interfere with his everyday activities. However, it can happen that the virus develops to an exceptional degree in the lung tissues themselves, where it attacks the cells lining the alveoli. It then becomes pneumonia, a serious and possibly fatal disease. This type of influenzal pneumonia is happily rare in children and adults in good health, but a chronic congestion of the lung (following a heart disease), pre-existing lung lesions, or pregnancy may provide a potential field for its development.

A complication of influenza that is often observed is a secondary bacterial infection of the respiratory passages and lungs. As previously mentioned, the virus destroys the protective layer of cells of the tract and causes microscopic desquamation. These microlesions may become infected, just as a scratch or a burn may become infected if not protected with an antiseptic substance.

Different types of bacteria may cause inflammation, but the most dangerous are the pyogenic cocci (certain families of streptococci and staphylococci), which are also the origin of inflammation in wounds and burns. An influenza patient who gets such germs in his nose or throat risks a serious infection of the respiratory passages and lungs. Nowadays, staphylococcal infection is much more common than streptococcal infection, which was predominant in the great epidemic of 1918. Influenzal pneumonia caused by staphylococci may quickly become fatal if it is not detected by bacteriological means in its early stages. It has recently been observed that patients suffering from boils (which are always caused by staphylococci) are less resistant to this illness because they are carriers of pathogenic staphylococci in the nose and throat. In a general way, secondary bacterial infection causes a feverish state in the patient which, if suitable measures are not taken, persists in a marked fashion for three or four days after the beginning of the illness.

Epidemiology

The epidemiology of influenza is a particularly interesting chapter in the history of research into infectious diseases. Soon after the discovery of the influenza virus in 1933, it became clear that the illness broke out in winter in both the northern and southern hemispheres and that every two or three years an epidemic broke out in Europe, America and Australia.

In response to infection, human beings develop antibodies that constitute a protection against subsequent infection. After experiencing a number of epidemics, many people are thereby provided with antibodies and it would be reasonable to expect that the immunity enjoyed by a large proportion of the population would prevent the infectious consequences of viral attack. It would appear, however, in our experience, that the influenza virus can overcome the immunological barrier by modifying its biochemical structure. In other words, it is capable of escaping the protective effect of natural immunity and thus of contaminating an important section of the population, especially children. A more or less comparable phenomenon is the ability of staphylococci (as well as other types of bacteria) to become resistant to antibacterial preparations (such as penicillin), so that in hospitals, where antibiotics are in regular use, new strains of staphylococci are continually appearing which become insensitive to these widely-used preparations. These structural modifications affecting certain strains of influenza virus were observed in 1934 and 1936, at least with regard to virus A. Another group, group B, showing analogous biological alterations, was identified in 1943 and 1959. Such modifications are always followed, after a short delay, by violent epidemics.

Pandemic influenza

Apart from normal epidemics of influenza, there exists an epidemiological phenomenon that is quite different and which is still mysterious; pandemic influenza. It has been known since the Middle Ages that two or three times in a century influenza, breaking out from a local centre, spreads rapidly to other regions, with a death rate that is four to eight times higher than that of winter influenza. Curiously enough, this pandemic influenza is quite likely to occur in summer. The last pandemic took place in 1957-1958. It broke out in the south-western province of China and, facilitated by modern air and sea transport, was rapidly transmitted to all parts of the world. Observed in China in February, the epidemic had overrun Indonesia by April and May. At the beginning of June, the first cases were reported in the Low Countries.

The virus responsible for pandemic influenza belongs to group A, but some of its properties differ so much from those of the A strains studied since 1933 that some research workers refuse to admit that it is derived from the A viruses in circulation before 1957. It is possible, they suggest, that this virus was present in certain unidentified animals which transmitted it to man.

A number of factors lead one to believe that a virus with the same characteristics caused the pandemic of 1889-1890, which was also of Asiatic origin. A number of earlier pandemics also appear to have come from China. Thus it is conceivable that an animal carrier of strain A inhabits this zone, especially as we know that an animal influenza exists.

The best-known example of animal influenza is that of the pig in the United States. All we know of this very interesting disease derives from the work of Dr R. E. Shope, of the Rockefeller Institute. The vector of the virus of porcine influenza is a worm living in the lungs of the pig. The illness occurs in the autumn and winter. Dr Shope firmly believes—and other virologists share his views—that porcine influenza originated the terrible pandemic of 1918, the mortality from which was sixteen times greater than that of 1957. This is probably because of the ability of this virus to attack human lungs. There are, however, very strong indications tending to show that it was man who, in 1918, transmitted the disease to pigs in America. Unfortunately, the source of this great pandemic has not been discovered. However, if Shope's theory has any foundation, and all these facts appear to confirm that it has, virologists have identified the viral factor of an extremely serious disease and from now onwards should be able to study it in the laboratory, in order to prepare vaccines capable of defending the human species in the event of a return of this scourge.

Therapy and preventative measures

So far, no antibiotic for directly combating the virus has been found. Fortunately, the progress of medicine has been such that we are well equipped to overcome secondary bacterial infection, which often accompanies viral infection; indeed, thousands of human lives were saved in the pandemic of 1957. Prophylaxis against influenza, which consists of inoculating killed virus, is reasonably efficacious, especially as a means of protecting the lungs. As a preventive measure, yearly vaccination is recommended with vaccines composed of different viral strains (A and B) for those suffering from chronic cardiac and pulmonary affections, as well as pregnant women and old people.

A great number of illnesses of the respiratory passages resemble true influenza. The techniques for combating the viruses responsible for these illnesses are very complex and at present only a small number of laboratories can use them. In this field a recent discovery of great interest is that of the common cold virus, the outcome of research carried out by Dr Tyrrel and his colleagues in the Common Cold Research Laboratory at Salisbury.

It is to be hoped that this microbial affliction, which causes numerous sinus and middle-ear infections every winter, will soon be overcome by using prophylactic measures. This victory, when it occurs, will also be a happy one for asthmatics, who are often badly affected by the slightest cold.

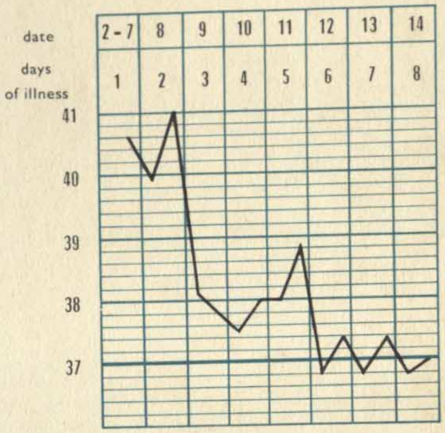

Fig. 4. Temperature chart of an influenza patient. After a very marked rise in temperature in the first two days, there is a recurrence of fever on the fifth day.

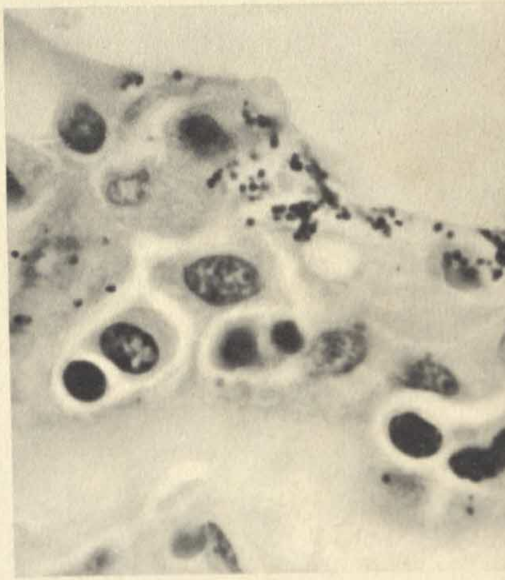

Fig. 5. At an advanced stage of influenza infection, the ciliated cells disappear, so that there is only one layer of replacement cells. Photograph taken when staphylococci (black spots) invade what is left of the epithelial covering. (Mag. × 2,000).

Acute rheumatic fever

Robert LAPLANE

The streptococcal origin[1] of acute rheumatic fever, suspected for many years, cannot now be doubted. Although lacking absolute formal proof, this belief is founded on a great number of coherent arguments. Some are clinical: for example, close observation has shown that the rheumatic crisis is almost always preceded by streptococcal angina; there also exists in all societies a remarkable parallel between epidemic waves of streptococcal infection and the outbreak of cases of rheumatism.

The search for haemolytic streptococcus[2] in the throat of rheumatic fever patients is positive only in one case out of two; this, however, is not surprising, since the interval that separates pharyngeal infection from rheumatic crisis is roughly two to three weeks, and this delay is sufficient for the germs to have been eliminated. The passage of these germs in the organism is marked indirectly by serological modifications; in 95 per cent of cases, the rheumatic crisis is accompanied by a characteristic rise in the number of antistreptococcal antibodies. Prominent among these are the antistreptolysins. Haemolytic streptococcus (Group A) has a number of antigens, some of which have the characteristics of exotoxins: streptolysin, hyaluronidase and streptokinase. Their diffusion in the organism entails the formation of corresponding antibodies.

The therapeutic argument is very impressive: systematic penicillin treatment of streptococcal infections of the pharynx completely eliminates the risk of rheumatic fever. Former sufferers can almost certainly be protected from relapse by the continued use of penicillin.

The haemolytic streptococcus A is thus well established as the responsible agent and its forty-nine serological types are of equal importance in this respect. Seventeen principal types were first isolated by Lancefield. The total is now forty-nine. However, we are far from having fully elucidated all the factors leading to the appearance of the disease.

Only in three per cent of cases taken at random does a streptococcal infection of the throat lead to acute rheumatic fever. However, a former rheumatic-fever sufferer runs a risk 40 to 50 per cent above the average that a streptococcal infection will cause such a fever. This contrast emphasizes the need for taking individual predisposition into account, but it is very difficult to give reasons for such vulnerability. To judge by the frequent appearance of this disease in the same families, it would appear to be congenital; but it is impossible to say more than this.

The appearance of acute rheumatic fever is generally sufficiently clear for diagnosis to present no difficulty. It is most often found in infants or adolescents (fig. 3) who, fifteen days after a quite ordinary pharyngitis, suddenly develop acute febrile polyarthritis. In a few hours, one or more of the large joints becomes swollen, inflamed, and very painful, the temperature goes up to about 102°, and the patient is soon in a very precarious condition. It is not that the infection itself shows a worrying development; from this point of view, it does not differ from many other diseases, but the diffuse arthralgia, made worse by the slightest movement, prevents sleep and even rest, and is sometimes almost intolerable.

This clinical picture is associated with a number of other biological modifications. These externalize the inflammation of the connective tissue and include acceleration of the sedimentation rate of the red blood cells, (which may exceed 100 mm in the first hour);[3]

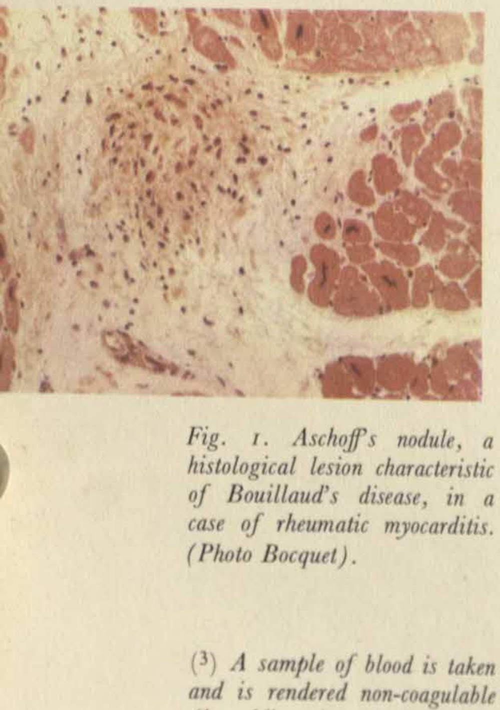

Fig. 1. Aschoff's nodule, a histological lesion characteristic of Bouillaud's disease, in a case of rheumatic myocarditis. (Photo Bocquet).

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(1) *The streptococcus is a bacterium of rounded shape, the individuals of which are grouped in short or long chains, according to the culture medium. It is transmitted from man to man by direct contact and also by means of damp or humid air containing fine droplets in which the germs may be adsorbed.*

(2) *Haemolytic streptococci are those that make a toxin that destroys red cells. These cause the most damage.*

(3) *A sample of blood is taken and is rendered non-coagulable (by adding citrate), then separated into its constituents (components and plasma). It is sufficient to note the depth of the residual plasma after one hour and then after two hours. The normal rate of sedimentation is*

Continued on next page

an increase in hyperfibrinaemia, which often reaches 10 g per 1,000; elevation of the level of different glycoprotein fractions of the blood serum; and electrophoretic disturbances[4] (fig. 4). These disturbances are not specific; their interest lies in the quite unusual intensity of the modifications observed.

Other biological modifications are evidence of streptococcal infection. In addition to the presence of these in the pharynx, which, as already mentioned, may be deceptive, attention must be paid to the level of specific antibodies in the serum—particularly of antistreptolysis. The blood picture does not alter greatly; usually, however, it shows hyperleucocytosis with neutrophil polyneucleosis.

Various manifestations may multiply the symptoms of rheumatism; their incidence is very unequal. Erythemas (redness of the skin) and subcutaneous nodules are found only in severe forms; respiratory manifestations (foci of pneumonia or pleurisy) are very rare. Even rarer are psychological or neurological troubles grouped under the name of cerebral rheumatism; nevertheless, the relation between rheumatism and Sydenham's chorea[5] is close, and it is not exceptional for these diseases to follow one another. But these manifestations are of little importance compared with cardiac sequelae, which, because of their frequency and terrible future consequences, represent the major complication of this illness.

Rheumatic myocarditis[6] may reveal itself in the characteristic picture of cardiac insufficiency: difficulty in breathing, acceleration of the heart-beat, olyguria, painful enlargement of the liver, and galloping arrythmia. This is exceptional, however, in cardiac effects of rheumatism; the rule is that usually it is inaudible and only a close examination of the heart can reveal it in time.

An attack on the myocardium is usually shown only by disturbance of rhythm or by anomalies in the electrocardiogram. The same is also true of pericarditis, which shows itself by a perceptible murmur on auscultation or by an increase in the volume of the heart, owing to the presence of liquid. Endocarditis, the most important of these conditions, is revealed by a muffling of heart noises or by the appearance of a systolic or diastolic murmur. Such murmurs may lead to a fear of valvular lesion; but at this early stage of the illness it would be premature to say that such a lesion exists.

The symptoms just described may be found grouped in various ways to give pictures differing in variety, complexity, and seriousness. Besides cases of medium intensity, in which the picture conforms to the classic description, exceptionally serious cases are sometimes found. Such cases are characterized by intensity of fever, worsening of the general condition, important articular symptoms, erythemas, which may result in conditions of septicaemia, heart attacks, often of a serious pancarditis type, and various visceral manifestations which justify great anxiety. However, treatment, if properly applied, may rapidly transform this situation.

Attenuated forms of the disease are very frequent in children and diagnosis may be difficult; following febrile pharyngitis, the appearance of transitory arthralgias (joint pains), which are not very intense and are without inflammatory symptoms, may or may not justify a diagnosis of rheumatism. It is permissible to hesitate—in such cases the search for biological disturbances may be of great assistance. These, however, are not specific and only really important changes are significant; slight unfavourable changes in biological constants do not decide the matter one way or the other. If in doubt, it is best, therefore, to prescribe precautionary treatment.

Modern treatment

Modern forms of therapy have completely altered the short- and long-term course of rheumatic disease. At one time, only salicylate treatment was available. The dose of this preparation is 8 to 10 g of sodium salicylate per twenty-four hours, plus 0·5 g for every year of age in children. This had a remarkable action on fever and arthritis, but it could not prevent cardiac complications, still less cure them; furthermore, there were forms of rheumatism that were resistant to salicylates. Above all, the frequency of relapses was a grave menace. Mortality was therefore high and cardiac sequelae were numerous among survivors.

The introduction of sulphonamides, of penicillin, and then of cortisone, has placed the disease in an entirely different perspective. Nowadays, treatment of a rheumatic crisis has a double aim: to sterilize streptococcal infection of the pharynx, and to eliminate inflammation of connective tissue. The first of these aims is accomplished by antibiotics, particularly penicillin (the dose of penicillin is 2,000,000 units per day for intramuscular

Fig. 2. A colony of haemolytic streptococci on blood culture medium. Note the discoloration of the culture medium, due to the haemolysing action of the germs. (Mag. × 70).

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2 to 5 millimetres in one hour. Acceleration of the rate of sedimentation indicates, generally speaking, an acute inflammation of connective tissue in any part of the body, even if the inflammation is not visible. Fibrinogen is the largest circulating molecule in the blood with a molecular weight of 900,000. Its concentration is increased in certain infections, such as acute rheumatic fever. The level is normally four to five grams per thousand.

(4) *The action of an electrical field permits the separation and quantitative determination of the protein fractions of blood serum. In rheumatism this electrophoresis shows a diminution of albumin and an increase of alpha 2 globulins and gamma globulins.*

(5) Sydenham's chorea *(or St Vitus's dance) is characterized by involuntary muscular contractions, occurring even during rest and causing a succession of extensive, rapid and unco-ordinated movements.*

(6) Myocarditis *is inflammation of the heart muscle itself.* Pericarditis *is inflammation of the external envelope of the heart.* Endocarditis *is inflammation of the fine membrane lining the internal cavities of the heart.* Valvulitis *is inflam-*

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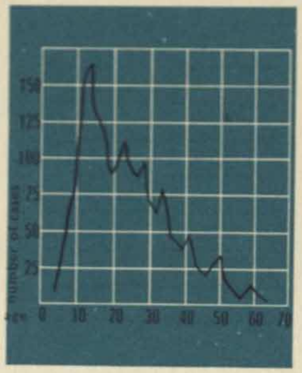

Fig. 3. Incidence of rheumatism according to age. The curve shows a clear maximum during late childhood (eight to fourteen years) after which the number of cases diminishes progressively (cited from Walgren).

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mation of the valves that prevent reflux into the heart cavities (between the auricles and the ventricles) and at the entrance of the large vessels (aorta and pulmonary artery) in the corresponding left and right ventricles. Pancarditis *is a lesion in all three of the cardiac membranes.*

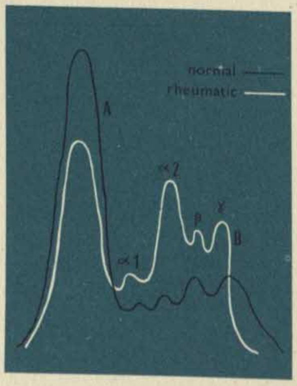

Fig. 4. Electrophoresis of blood serum proteins in a normal individual (A) *and in a patient with acute rheumatic fever* (B). *Note the appreciable differences in the level of alpha 1, alpha 2, and gamma globulins.*

injections); the second entails the use of a number of anti-inflammatory preparations: cortisone[7] and its derivatives, and salicylate and pyrazolate derivatives.

Application of this treatment has a spectacular effect: in a few hours the fever abates and at the same time the articular symptoms recede; the next day, a patient who was a weak, complaining sufferer finds his pains reduced, feels relaxed and is out of his miseries. This feeling of being free from disease is amplified on succeeding days and the patient is astonished at being kept in bed and under treatment when he believes himself to be cured.

In fact, and in spite of appearances, the illness is not over, and this is proved by the development of the biological symptoms. It is true that the slowing down of the sedimentation rate, noticeable at once, continues regularly, so that in a week or a fortnight a normal picture is obtained; but the reduction of most of the other biological symptoms of inflammation takes much longer. If treatment is stopped too soon, a relapse is to be feared, marked by the reappearance of fever, articular symptoms, and a renewed rise in the high sedimentation rate. In such cases, a new application of treatment is required. Sometimes, however, a renewal of the disease is slight and spontaneously curable. Here we have a 'rebound' phenomenon, very often observed when cortisone treatment is stopped.

It is not always easy to foresee what should be the minimum duration of anti-flammatory treatment, since neither the intensity of biological or clinical symptoms, nor their development under treatment gives any formal indication. Four to eight weeks appears on an average to be a reasonable time; but each case must be judged by its own symptoms and the doctor must adapt treatment to individual requirements.

This form of treatment has a preventive action, particularly on cardiac complications. In order for it to be efficacious, early treatment is therefore essential. It can cause a regression of pericarditis, myocardial inflammation, or incipient valvular involvement, though cardiac murmurs are apt to disappear spontaneously though, inversely, certain valvular lesions become apparent only later. A valid estimate of cardiac sequelae can only be made at the end of six or even twelve months; on this basis they appear to affect about one patient in five.

Formerly, the outlook for rheumatic patients was dark because of the frequency of relapses. The human organism does not easily acquire immunity against streptococcal infection and this is so widespread that the risk of re-infection is almost permanent, especially in large communities. Spontaneous vulnerability of rheumatic patients can be estimated from the following statistical data. An individual who has had an attack of rheumatism has one chance in two of relapsing if he becomes re-infected with streptococci; and some 60 per cent of former rheumatic fever sufferers have a relapse during the five years following the first attack.

Much has already been done to remove this heavy burden through the curative treatment of streptococcal pharyngitis by antibiotics. These are applied systematically in cases of previous rheumatic illness and reduce the incidence of the risk of relapse by 80 per cent. However, a better result, since it almost approaches 100 per cent, may be achieved by continuous prophylaxis. Nearly all doctors have come round to this point of view. This protection could be ensured by sulphonamides, but in practice penicillin has shown itself to be preferable; it is more reliable and presents fewer inconveniences. Two preparations may be used with equal success: oral penicillin taken daily, and slowly eliminated penicillin injections of one dose every two or three weeks. It goes without saying that the protection provided by this treatment is efficacious only if it is maintained really continuously over a number of years. How long the treatment should be kept up is not yet universally agreed upon, but five years would appear to be a reasonable time.

Satisfaction is justified in view of the therapeutic progress from which rheumatic sufferers have benefited. It nevertheless remains to fill in the gaps. It is possible that the passive immunity enjoyed for some years by rheumatic sufferers may impede the acquisition by them of a natural and durable immunity. It is to be hoped that in time it will be possible to prevent not only relapses but also initial attacks of rheumatic fever. The discovery of preventive vaccination would provide a neat solution of the problem of total prevention. Only a small number of individuals are apt to develop rheumatic fever. In order to protect this minority it is desirable that a way should be found to distinguish them from others, ie, to discover evidence of the 'rheumatic temperament', about which as yet we know practically nothing. So long as these problems remain unsolved, research must continue uninterruptedly.

(7) *Cortisone (17-hydroxy-11-dehydro-corticosterone acetate) is administered in the form of cortone, the dose being 25 to 30 mg per day.*

Poliomyelitis

Stéphane THIEFFRY

Of all virus diseases, poliomyelitis during the past fifty years has caused the greatest interest and led to the most intense research. The disease is still spreading and is found today in every continent and country of the world. It seems to mock improvements in sanitation, and increases in frequency and gravity while all other infectious diseases are decreasing or disappearing. Countries which have reduced the danger of tuberculosis and lowered the level of infant mortality to a minimum are, ironically, those which have had the worst experience of poliomyelitis.

This disease is doubtless as old as man. That it should have been identified only during the last hundred years may seem surprising. 'How is it,' said Charcot, 'that one fine morning, Duchenne discovered a disease that probably existed at the time of Hippocrates?' What really seems to have happened was that the end of the nineteenth century and the beginning of the twentieth witnessed the outbreak of widespread epidemics just when medicine was beginning to move away from purely empirical methods and was finding its way along clinical and anatomical lines. Meanwhile, the work of Pasteur in the biological field was revolutionizing the concept of infectious disease.

It was a German orthopaedic surgeon who discovered infantile paralysis, and a Swedish paediatrician who defined the characteristics of the disease and described its multiple forms. Thus a new entity made its appearance—poliomyelitis—sometimes still called Heine-Medin's disease, after these two early research workers.

The seat of the illness was shown for the first time by Vulpian to be in the spinal cord, or more precisely, in the large nerve cells of the anterior horn. The infectious origin of the disease was finally accepted in 1908, with the announcement by Landsteiner of the transmission of poliomyelitis to a monkey; from then on, a new approach to the study of the disease was started. By experimenting on monkeys and certain other animals, we were able to complete our knowledge of poliomyelitis viruses—their mode of action and dispersal and the reactions of the organism in which they are to be found. This 'monkey era' has lasted for more than forty years.

The most important advance recently was the announcement, in 1949, of the cultivation of the virus *in vitro*. This we owe to John Enders, of Boston. The extraordinary simplification of techniques, giving laboratory virology a routine status, has led to the definition, aetiology, nosology,[1] epidemiology and immunology of poliomyelitis.

Virological studies are now sufficiently well advanced for viruses not only to be isolated and identified (or even figured, thanks to the electron microscope), but also grouped in families. Using this systematic approach, the viruses responsible for poliomyelitis in man have been classified among the enteroviruses. Three types of virus responsible for human poliomyelitis have been identified, ie, types I, II and III, also designated by the names Brunehild, Lansing, and Léon, respectively. The first and the last are the names of the monkeys used for the isolation of these types. Lansing designates the locality where type II was discovered by Armstrong (1939). The Lansing strain is remarkable for the fact that it is equally pathogenic to a breed of rat *(Sigmodon hispidus)*, as is the Léon strain to a new-born mouse. These particular animal sensitivities, before *in vitro* cultivation and together with crossed immunity tests, enabled the strain to be identified. Today, typing is made very easily *in vitro*. The addition to the culture medium of a standard serum containing neutralizing antibodies stops the develop-

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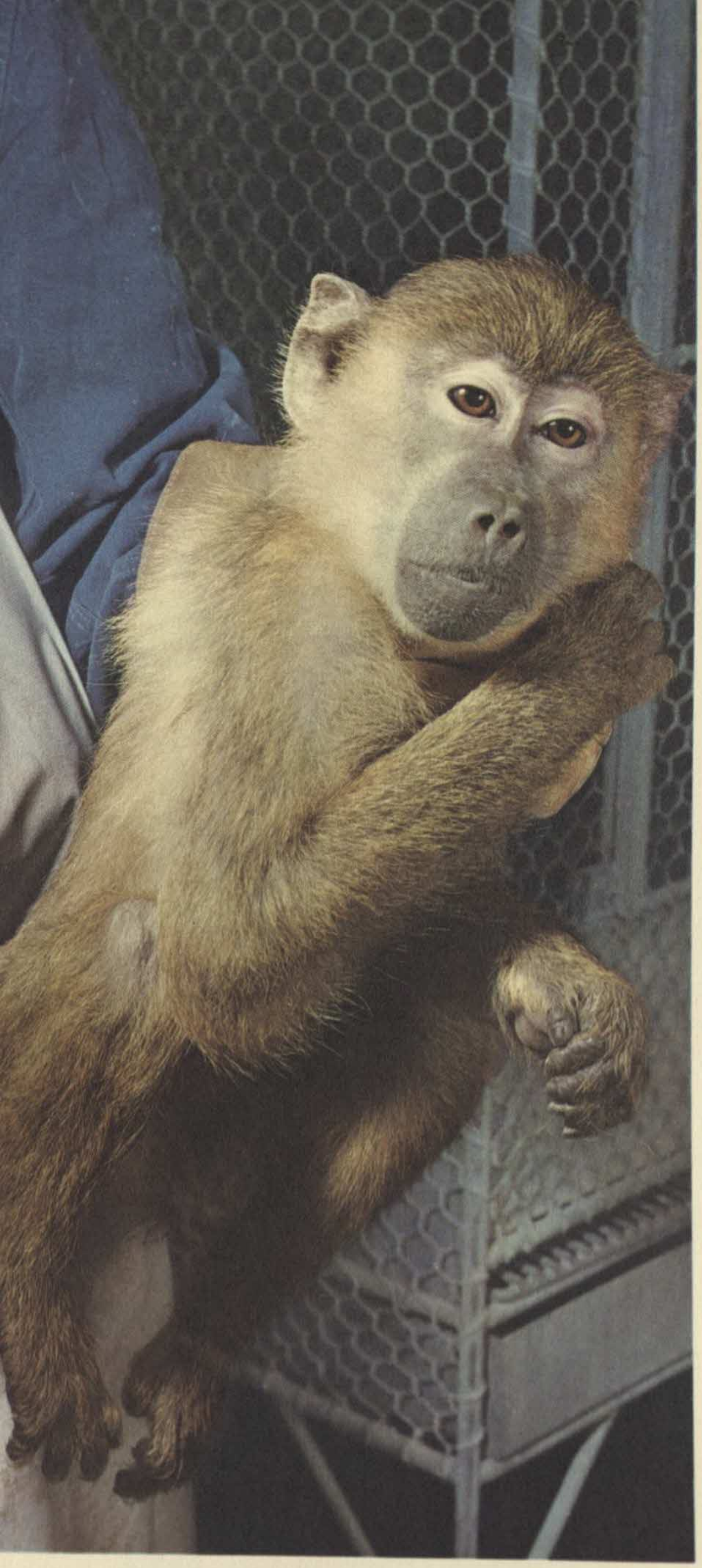
(1) Nosology: *the study of distinctive characteristics which classify diseases.*

(2) *Hence the name of the disease: acute anterior poliomyelitis—inflammation of the anterior horn of the grey matter of the spinal cord. In fact, cells may also be affected in that part of the spinal cord called the anterior grey column.*

(3) Motor unit: *a motor cell of the spinal cord, its prolongation (or nerve fibre), and the muscle cell (or fibre) that it innervates. The entire peripheral system of voluntary muscles is based on the juxtaposition of motor units (see diagram, p. 37).*

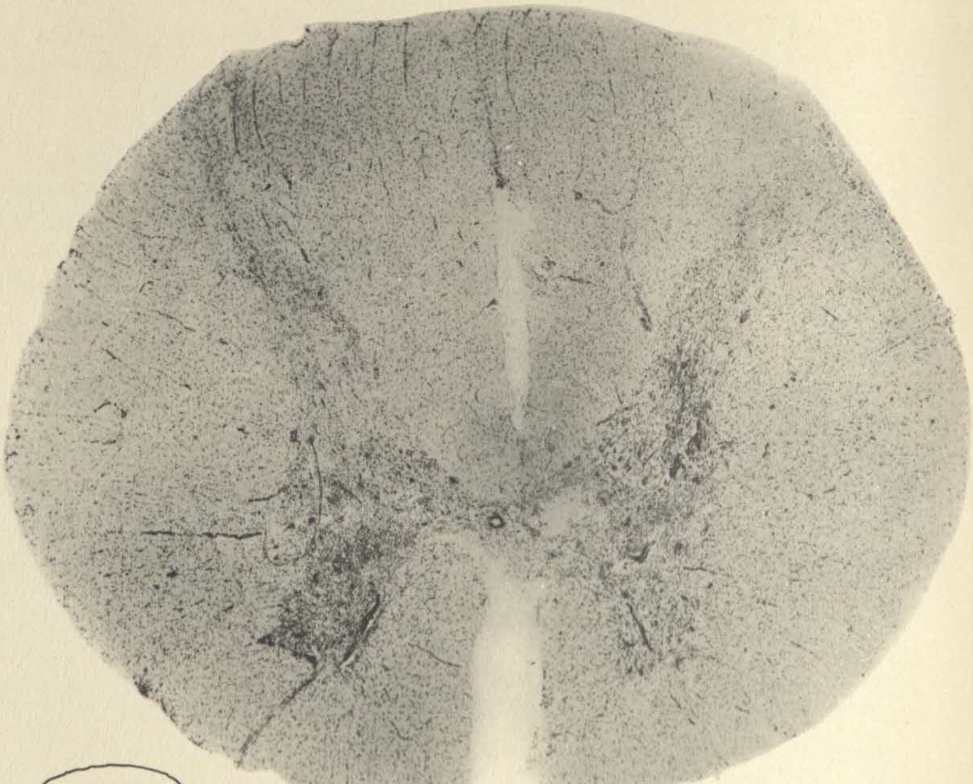
(4) *This tendency to regression is explained by certain motor cells not being destroyed but only injured. They may slowly regenerate and reinnervate the muscle fibre that corresponds to the cell. Recoveries may also be explained by compensatory hypertrophy of the intact muscle fibres in a muscle that is not completely paralysed. Suitably controlled muscular exercise favours this compensation.*

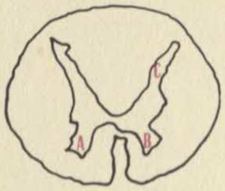
(5) *At each respiratory movement, a quantity of air penetrates into the alveoli of the lungs on inspiration and an equal quantity leaves on expiration. Lung ventilation is the amount of air which has been in contact with the lung alveoli per minute. Pulmonary ventilation provides oxygen for the blood and eliminates carbon dioxide in a way that is perfectly adapted to the needs of the organism. Diminution of ventilation leads to an impoverishment of* O_2 *('hypoxia') and to an excess of* CO_2 *('hypercapnia'), causing asphyxia.*



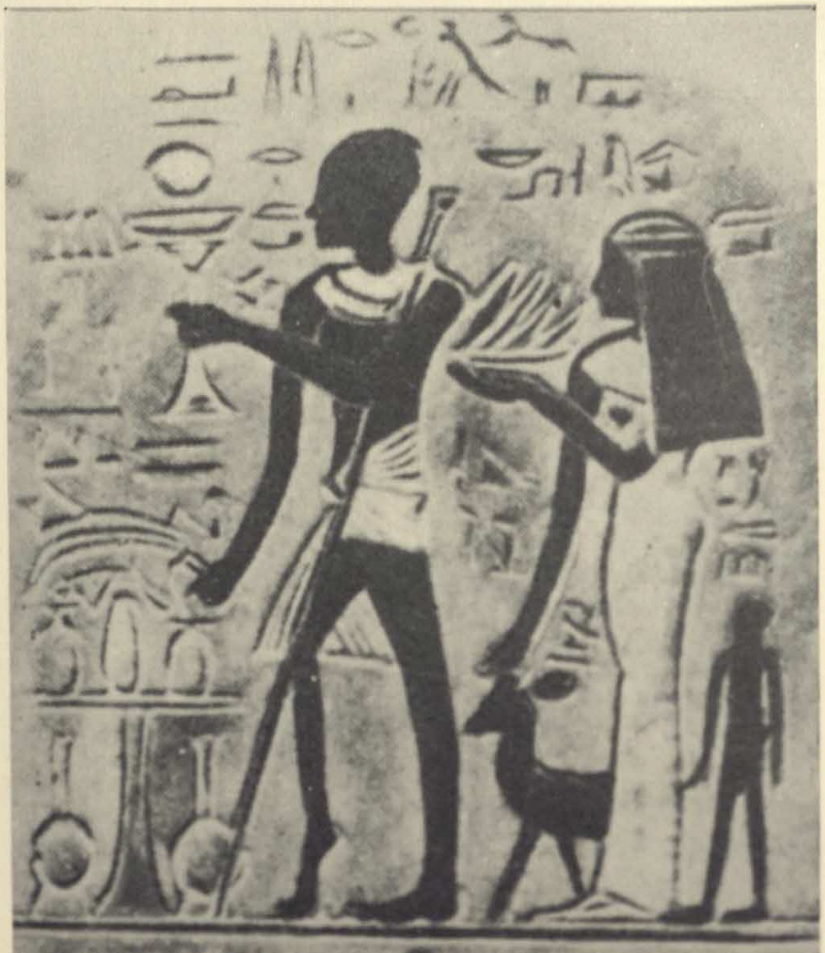
The Macaccus rhesus monkey is of great help to man in the production of poliomyelitic vaccine; the virus of the disease is injected into the animal's kidneys and it is from this organ that the vaccine is made. (Photo Lod, Pasteur Institute, Garches).

Although poliomyelitis has been the subject of world-wide investigation only during the last fifty years, it is one of the oldest-known diseases: an Egyptian bas-relief, dating from 1300 B.C., shows a man with muscular atrophy of the right leg, characteristic of the disease. (Copenhagen Museum).





Section of the spine of a poliomyelitis patient. The drawing (left) shows the three sites of degeneration; the predominant lesion is in the anterior horns A and B. Notice in the photograph the less dark patch in horn B, where many cells have already been destroyed. The dark areas A and C indicate the violent inflammatory reactions diffusing throughout nearly the whole of the spinal cord at the start.



ment of the virus. The infected tissue cells remain intact instead of being destroyed, ie, lysed by the virus.

Poliomyelitis virus is spread over the whole world. Highly resistant to natural agents, it uses water as its habitat. It invades the human body in a manner which is either semi-permanent and relatively unobtrusive, or at certain periods its attack is massive and severe. This type of invasion coincides in all latitudes with the warm months of the solar year.

The virus, after its passage and multiplication in the human body, is eliminated in the faeces, thus dispersing again into its natural habitat. This is the virus cycle in nature, in which man forms an unlimited reservoir.

It is not known how man becomes infected or which path the virus takes once it has penetrated the barrier of the human body. However, it is known that when the virus penetrates the body, it causes an immediate and specific defence reaction. Poliomyelitis is no exception to the general biological law according to which the introduction of an antigen (in this case the virus) sets off the production of antibodies (here the neutralizing antibodies).

Present-day possibilities for cultivating the virus at its exit from the human body, or for tracing the ineffaceable path of its journey through the body by means of research and titration of antibodies, allow us to demonstrate rather than merely to guess at the course of an epidemic at a 'diffusion-period point' of the disease.

Symptoms and prognosis

Surprisingly enough, many people harbour the virus for a number of weeks and then eliminate it, acquiring specific antibodies and, in brief, displaying the biological signature of the disease without having the slightest symptom of illness at any time. To borrow a phrase from Charles Nicolle, the infection is hidden throughout and will remain so. It is in this hidden form that the greater part of humanity contracts the disease, and this is fortunate, because they thus acquire immunity, at least to this particular virus, without becoming ill.

During epidemics the same immunity is acquired by other human beings at the cost of a slight illness. They suffer a few days of fever, slight headache, and some digestive troubles which may seem to indicate angina or influenza. Sometimes a few more disturbing symptoms may suggest meningitis. In exceptional cases a more definite picture emerges and, in the atmosphere of an epidemic, diagnosis of the disease may be strongly suspected and the worst is to be feared. Yet no permanent serious damage results; the patient recovers, and a fresh invasion will definitely have been prevented.

However, a third category of patients does not fare so well. With these the virus penetrates deeply into the body and attacks the nervous system. The attack is localized, with a singular preference being shown for certain cells of the grey matter of the spinal cord at the point where it spreads out to form the anterior horn.[2] These cells all have the same physiological function, ie, to ensure contraction of the striped muscles of the organism by means of impulses transmitted to the muscle cells by a network of fibres (motor units).[3] The destruction of a motor cell by the poliomyelitis virus causes paralysis of the corresponding muscle fibres. The more of its motor cells that are affected, the more serious is the paralysis of the muscle. Again, the longer the lesion in the anterior horn of the spinal cord, the greater the number of paralysed muscles.

The development of the disease in its paralytic form is very regular. It begins suddenly with fever, headache, and vomiting. Then, after some days, a group of symptoms appear, sometimes enabling a diagnosis to be made during this phase and before paralysis occurs. The most outstanding of these symptoms are: a sharp pain in the back, pain caused by movement of the lower limbs, stiffness due to meningeal inflammation accompanying the attack on the spine, often difficulty in urinating, and somnolence.

The position becomes quite clear as soon as paralysis occurs; this extends and worsens a few days later. The extent of paralysis is variable and may consist of total paralysis of all four limbs and the trunk, or just of single muscles. Also, the degree of paralysis varies from discomfort to complete helplessness. Present-day techniques of neurological examination permit exact calculations to be made of 'muscular balance', which is indispensable to any approach to treatment.

Setting up muscular balance means observing the existence and degree of paralysis in each muscle (every muscle being numbered in accordance with a code established by international conventions). This codified appraisal, gives the doctor essential information. Poliomyelitis, though it has a preference for certain muscles such as the deltoid, which raises the arm, or the anterior calf muscle,

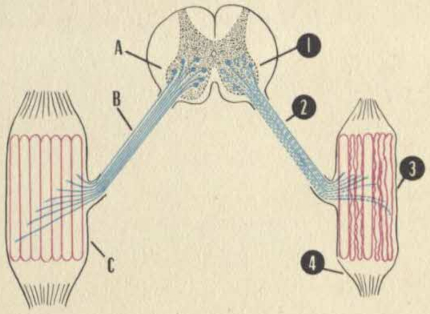


Fig. 1. This diagram represents an assembly of motor units, on the left, in a normal person; on the right, in a polio patient. A: transverse section of spinal cord. B: motor-nerve fibres. C: muscle made up of a group of muscle fibres. In the polio patient the anterior horn cells of the spinal cord are destroyed (1); the corresponding nerve fibres degenerate (2); muscle fibres (3) atrophy, and the muscle (4) is paralysed.

(6) *A number of mechanisms intervene in the causation of hypoventilation: (a) the virus may affect the motor cells of the muscles involved in the mechanism of respiration—diaphragm, intercostal muscles and muscles of the abdominal wall. The 'bellows' that cause inspiration and expiration no longer function, or do not function properly; (b) secretions may accumulate in the bronchial tubes or in the trachea, so that air can no longer reach the alveolus because of this obstruction; or the obstruction may occur higher up in the pharynx, in the not exceptional case where there is paralysis of deglutition and the patient cannot swallow; (c) the virus may sometimes injure a centre in the medulla oblongata that controls rhythm, depth and efficacy of respiratory movements.*

(7) *The first method known was the* iron lung. *The patient is enclosed up to the neck in a box, inside which bellows cause variations of pressure, which, transmitted to the thoracic walls, reproduce respiratory movements.*

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A more complex method, which has revolutionized the treatment of respiratory poliomyelitis, has been devised by Professor Lassen, of Copenhagen. The trachea is opened, and through the aperture thus made a tube is inserted that descends into the trachea; this tube is connected to a complex respiratory machine (Engström's apparatus) which enables insufflation and exsufflation of the volume of air required for correct respiration at appropriate pressure. The principle of the rocking bed *is to use the weight of the abdominal organs to stimulate the diaphragm artificially.*

(8) *In order to vaccinate a person, an infectious agent (antigen) is treated so that it loses its toxic property of damaging the organism (pathogenic action) but preserves the property of starting up a protective reaction in the organism (this is shown by the presence of antibodies). In order to prepare killed vaccines, treatment of the antigen may be obtained in various ways. The one most used since the discovery of anatoxins involves the combined action of heat and formaldehyde.*

(9) *Living vaccine inoculation consists of introducing into the organism a microbial strain chosen with great care from among those which, without causing disease nevertheless induce an immune reaction. The classic example is B.C.G., non-pathogenic tuberculous bacillus (Calmette and Guérin). Living poliomyelitis vaccines are made up of a mixture of the three non-pathogenic strains that are capable of producing immunization. Their introduction into the digestive tract, where they multiply without causing any trouble, produces exactly the same effect as natural hidden infection.*

which lifts the foot, may attack any muscle of the limbs or trunk capriciously and at random. Each patient, therefore, presents a special problem. Examination is concentrated on certain key muscles which are important in standing or walking. It is thus possible to form a rapid and approximate opinion on the favourable and unfavourable factors in the situation. The most important muscles are those of the trunk, such as those forming the abdominal wall or flanking the vertebral column (the spine), muscles which, if even slightly affected, may lead to spinal curvature. Paralytic scoliosis is one of the most serious complications in poliomyelitis. The degree to which the muscles have been affected must be studied with great care, if necessary by the use of electrical registration of muscular contraction (electro-myography). Any residual activity in the muscle, however slight, still persisting after a month of the disease, entitles one to hope for some improvement under well conducted treatment. But if a muscle has been radically affected, the chances of recovery are very slight. Estimates of future functional movement must take other factors into account. It has been known for a long time that poliomyelitic paralyses have two main characteristics: early muscular atrophy and a tendency to regress.[4] One of the greatest dangers to a paralysed patient is for him to remain immobile; this will lead to atrophy, muscular retraction, a distorted position of the body, deformation of the limbs and the vertebral column, and arrested growth of the paralysed limbs.

Treatment and rehabilitation

These dangers can be avoided, however, and remarkable recoveries and sometimes even complete cures can be achieved by the patient being kept under proper orthopaedic observation, rehabilitation adapted to his case being started as soon as possible. The re-education of movement by exercise is an outstanding branch of modern medicine. Kinesiatrics, which began with poliomyelitis, has now been extended to other diseases. It is based on passive, and later, on active movement directed and controlled according to precise rules. Re-education is applied during the first stage to the muscle itself, then later to re-learning natural movements and gestures. Applied early, carefully continued with the participation of the patient himself and pursued for a long period (seldom less than several years), the method ensures, in most cases, re-integration into school, family, or professional activities. Treatment of a complicated or serious case can only be carried out properly in specialized centres.

Important though it is, this part of the treatment, which tends to reduce to a minimum the seriousness of the infirmity, is only one aspect of the problem. In a large proportion of cases, poliomyelitis, from the moment it begins, may endanger life itself. Death supervenes because of a lack of or failure in respiration, following a rapidly progressive and fatal asphyxia, if lung ventilation sinks below the limits required for life.[5] There are various causes of reduction of ventilation in poliomyelitis, and they need to be specified in order that correct treatment may be given.[6]

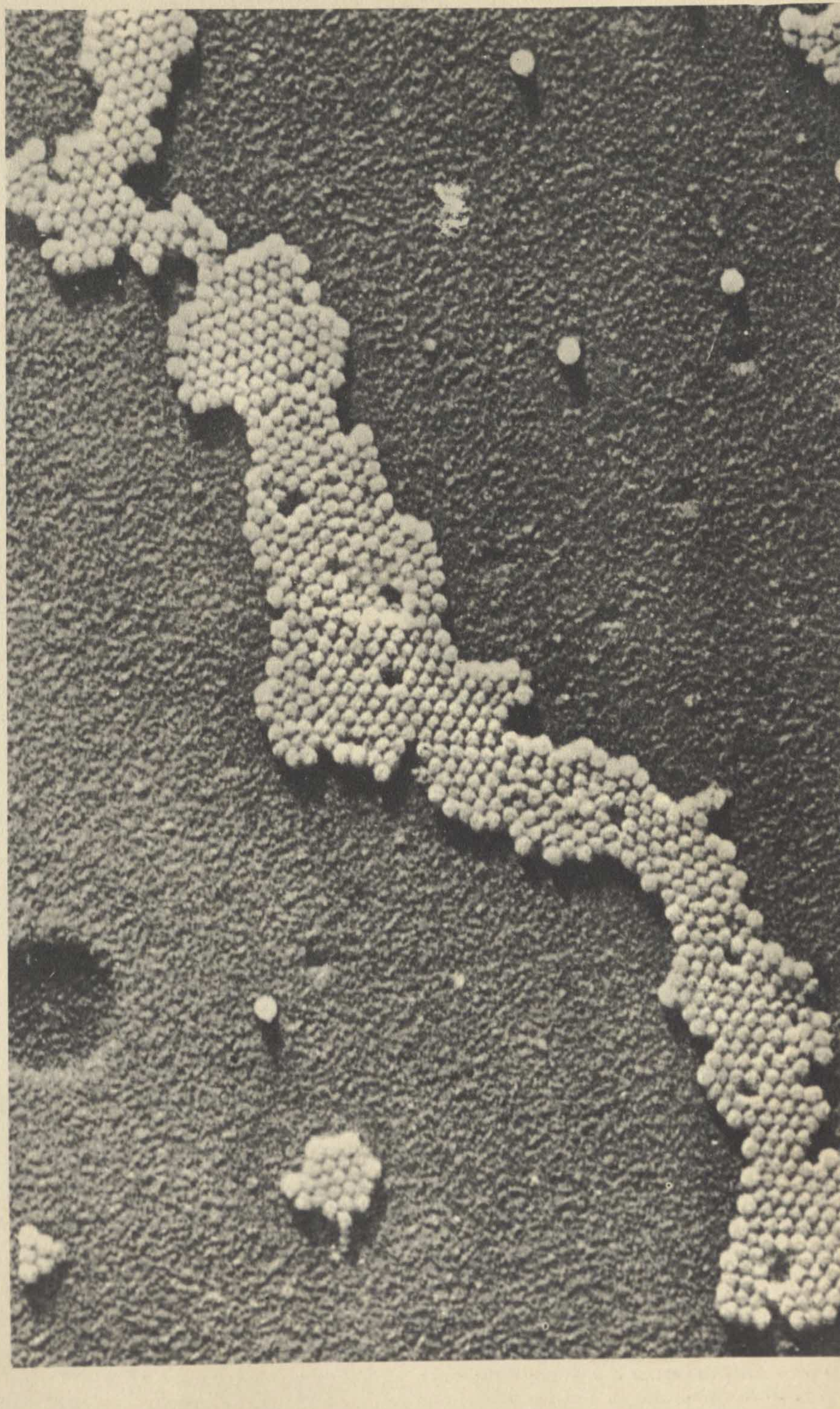
The essential information required for immediately starting treatment can result only from methodical examination: the 'clinical balance' of the respiratory muscles (intercostal and diaphragm muscles); the study of respiratory movement by radiography; the ability to swallow; and the study of 'chemical balance' in order to appraise humoral disorders linked to the accumulation of carbon dioxide in the blood. A careful study is essential because many respiratory insufficiencies cause little apparent disturbance and only become obvious after they have become irreversible or difficult to deal with.

In cases of this sort, every effort must be made to apply the only treatment there is: artificial respiration. All processes may be used, including, in cases of extreme urgency, hand-operated artificial respiration. Fortunately, technical achievements have made this task considerably easier. Respiration machines[7] can achieve remarkable results by ensuring controlled respiration over long periods. Choice of method, clinical and 'chemical' supervision of the patient, and respiratory re-education techniques, can be guaranteed only in highly specialized well-equipped neuro-respiratory re-animation centres. In such centres most patients are saved from a terrible death, and sufficient autonomous respiration can usually be re-established.

This brief survey of the essential requirements for correct treatment of paralysis—whether it be a matter of saving the patient by re-education over a very long period or by life-saving techniques that are difficult to apply—shows how heavy the cost of this disease may be, which is caused by one of the smallest viruses known.

For a long time, therefore, attempts were made to protect whole populations against the poliomyelitis virus, but ignorant as we are of

The electron microscope enables us to observe the poliomyelitis virus. The curious aspect of this virus is to be seen here. (From The Scientific American, *photograph by Dr A. R. Taylor, Park Davis & Co., Research Laboratory, Detroit).*



the real conditions of its propagation and contagion, these attempts were only partially successful. It was hoped that a method of vaccination would be found, but this had to wait until the culture of the virus made it possible to attack the problem under the necessary conditions of safety, security and innocuousness.

Anti-poliomyelitis vaccination

From that moment, the preparation of vaccines against poliomyelitis was based on methods and procedures which had already been tested in bacterial diseases. In 1954, a trial of a killed vaccine,[8] ie, Salk vaccine, took place in the United States. Owing to its success, in most countries of the world, and in particular in Western Europe, vaccines of the Salk type have been largely used.

More recently, after exhaustive laboratory studies, Sabin recommended the use of a live virus vaccine.[9] Millions of people, especially in Central and Eastern Europe, have been subjected to this form of vaccination. It must be recalled that living anti-poliomyelitis vaccines have the peculiarity of spreading from a vaccinated person, thus producing a secondary diffusion which reaches a large number of people.

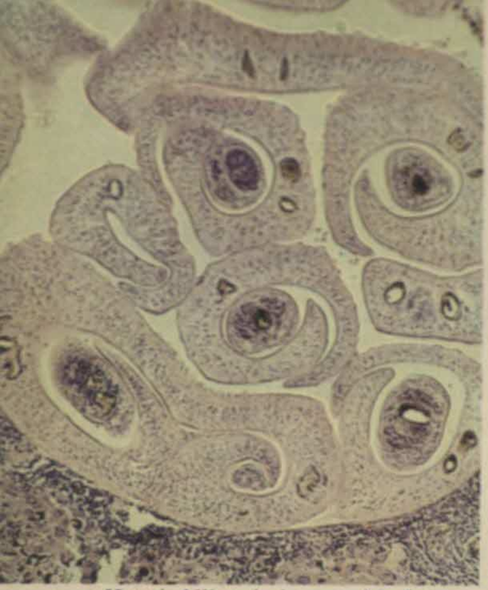
The large-scale experiments taking place throughout the world with one or other of these methods have, on the whole, been successful. The innocuousness of these vaccines is certain and their efficacy is undoubted.

However, as frequently happens, the experience of several years has revealed a certain number of problems. For example, there is the choice of vaccinating strains that must necessarily represent the three viruses; the possibility that 'antigen competition' *in vitro* may occur; the natural conflict that may arise between living polio viruses and other enteroviruses; and the difficulties of appreciating the real efficiency of vaccination following interference with natural infection.

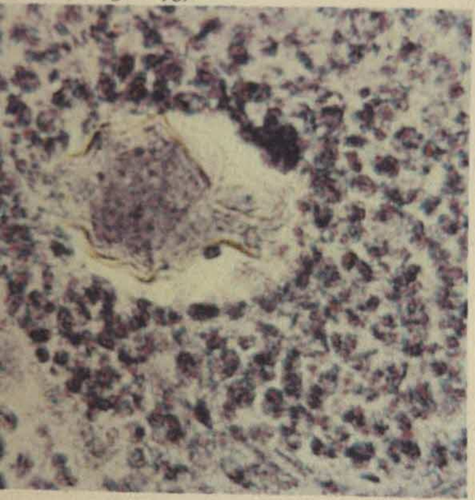
Nevertheless, the more than encouraging results of the vaccination campaigns that are now going on all over the world on hundreds of millions of children and adults give rise to immense hopes. If they are realized, it will be the end of a nightmare for humanity.

Diseases caused by parasites

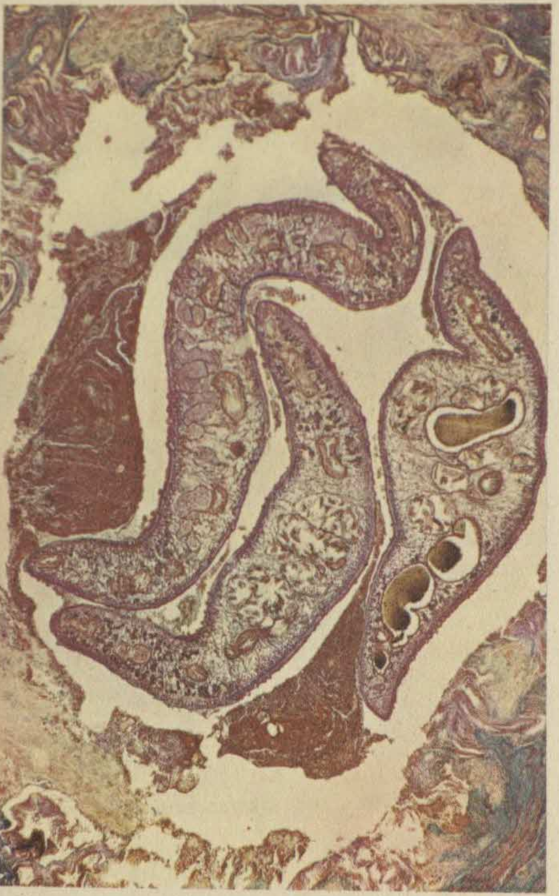
Besides disorders caused by micro-organisms, many serious diseases are caused by animal or plant parasites introduced into the tissues and inflicting great damage. These photographs show some characteristic aspects of these diseases. (Photo Lod, taken at the Parasitology Laboratory of the Paris Faculty of Medicine; preparations by Professors Galliard and L. C. Brumpt).



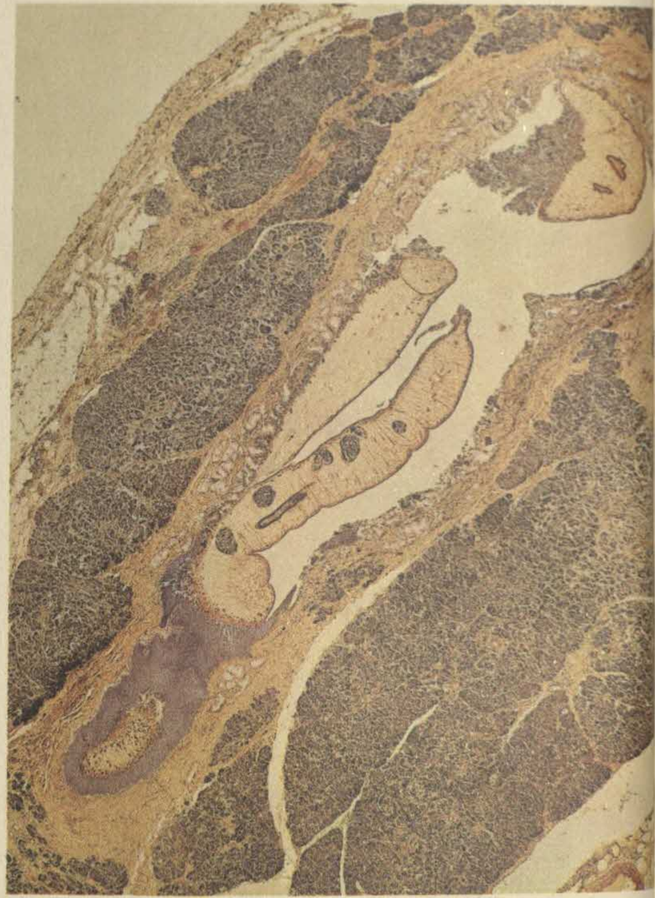
1. Hepatic bilharziasis, caused by Schistosoma mansoni. *These parasites are trematodes of separate sexes; about a dozen worms are shown in section in a portal vessel of the liver. The couple in the centre are typical: the lightly stained male, curled like a leaf encloses the darker stained cylindrical female. Adults are less irritating to the tissues than eggs; the latter cause bilharzial cirrhosis. (Mag. ×75).*



2. The Schistosoma *egg is tolerated much less than adult schistosomes. Fixed in a capillary vessel, it causes inflammatory reaction of a granulomatous type. When this reaction is produced in the intestine by* Schistosoma mansoni, *or in the bladder by* Schistosoma haematobium, *it facilitates elimination of the eggs in faeces or urine, and thus the completion of the life cycle. When eggs accumulate in the terminal hepatic ramifications of the portal system, they cause hepatic bilharziasis with hypertension. (Mag. ×780).*

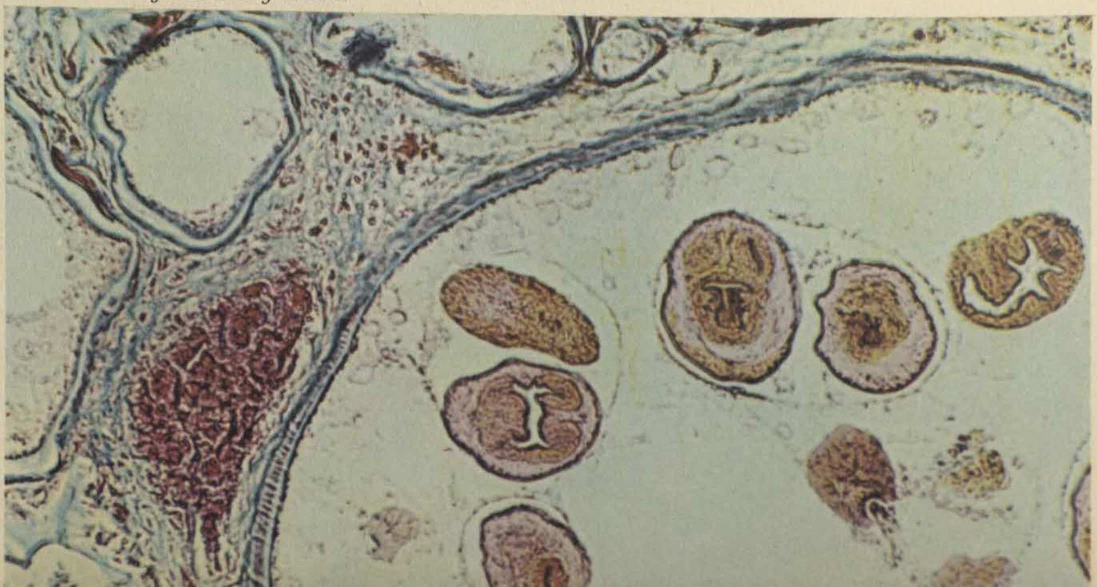


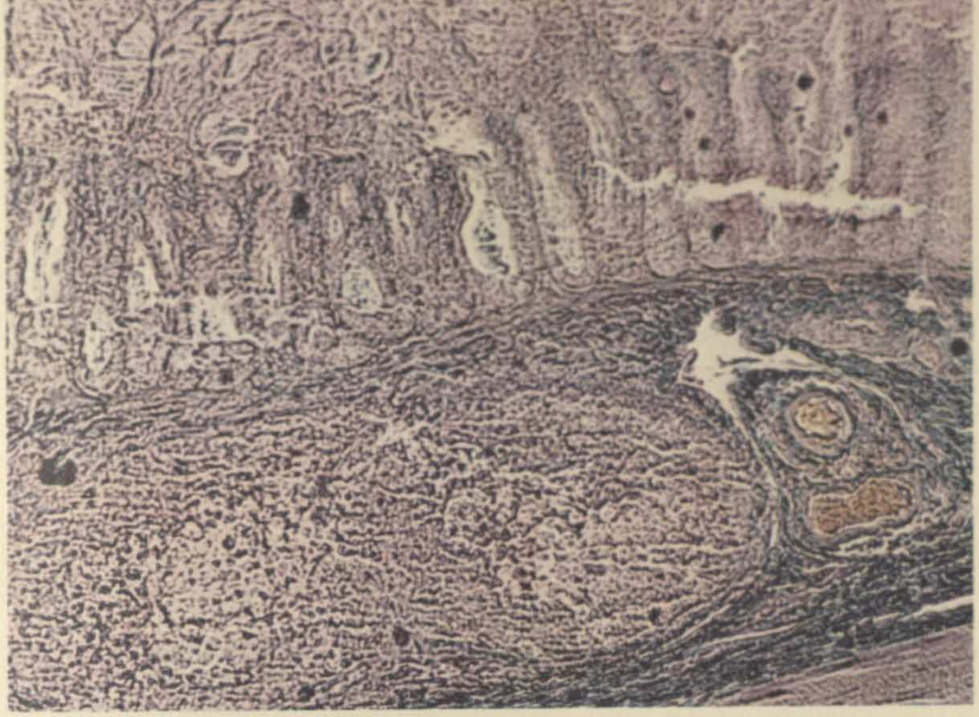
3. Hepatic distomatosis caused by Fasciola hepatica. *The flukes are hermaphrodite trematode worms. The large fluke lives in the bile duct of herbivores and causes sclerosis of the walls and adenomatous transformation of the epithelium. These lesions facilitate infection of the biliary channels and lead to the formation of calculi.*

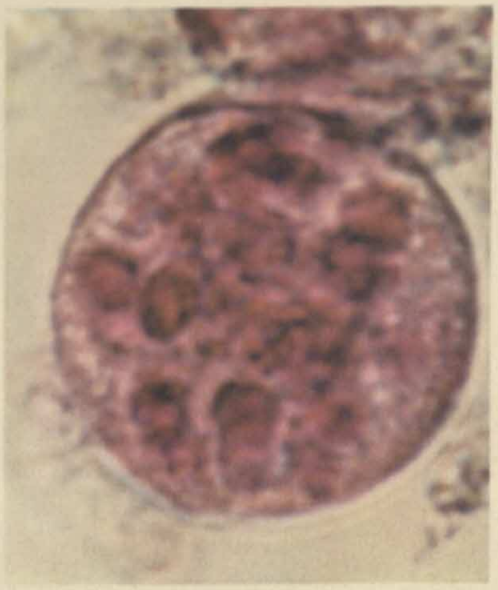


4. Distomatosis of the pancreas caused by Clonorchis sinensis. *These Chinese flukes can install themselves in the pancreatic ducts. The normally cylindrical epithelium of the pancreatic duct shows a pseudo-acinous mucoid metaplasia. Cancerous changes are possible. (Mag. ×20).*

5. Alveolar hydatic cyst of the liver: a large larva of Echinococcus multilocularis, *a small tape-worm that lives in the small intestine of the fox, the final host. The latter is infested by eating intermediary hosts, small rodents such as voles. Man accidentally becomes an intermediate host by eating strawberries, raspberries, or bilberries that have been soiled by foxes. In the section shown on the right, the scolex or invaginated taenia heads may be seen. (Mag. ×150).*





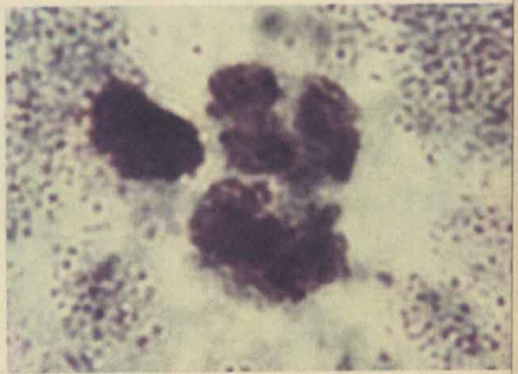


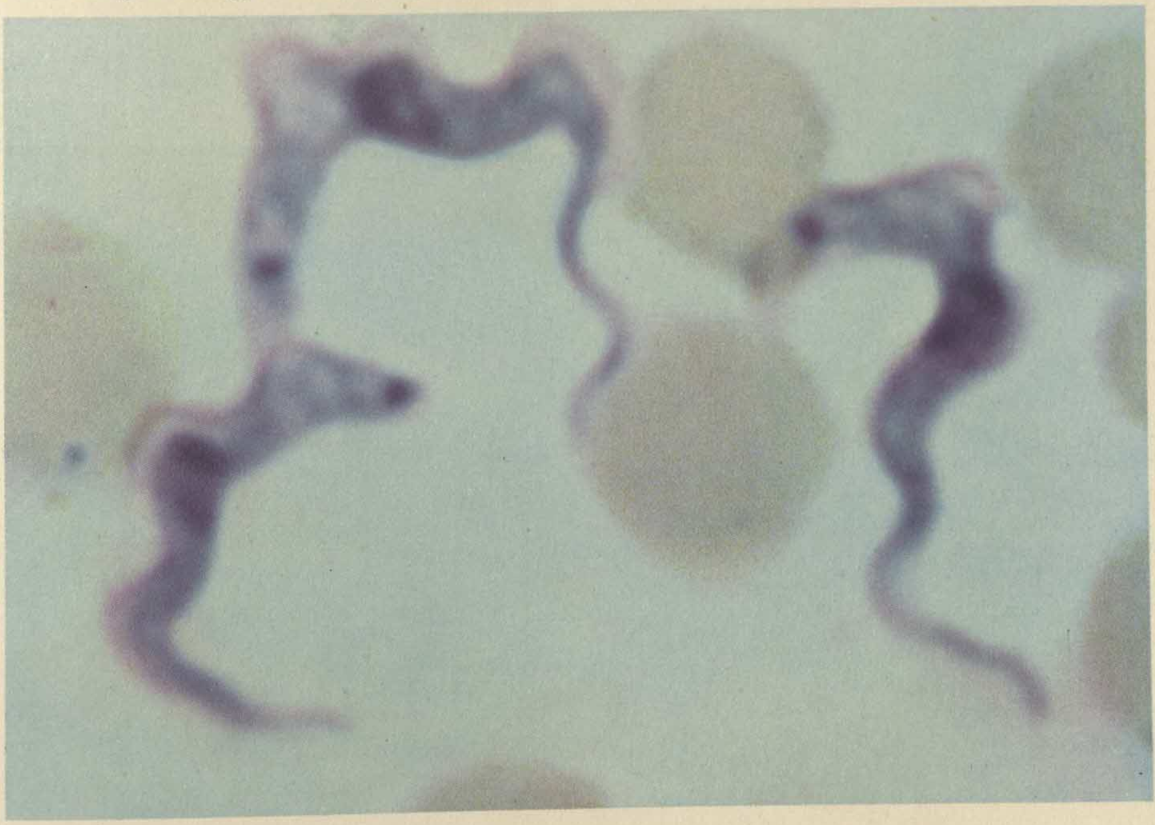
6. Section of intestine showing amoebic dysentery. Above, the mucosa is ulcerated and groups of amoeba have insinuated themselves between the glands. Below, the amoebae have invaded a lymph follicle which will open into the intestine after breaking the muscle layer (shown in the centre); there will then occur the classic picture of an amoebic abscess. (Mag. × 130).

7. Detail of the preceding section: Haematophage amoeba. Haematophagy and hystolysis are two basic characteristics of Entamoeba dysenteriae, *the only pathogen among seven different species of amoebae parasitic in man. The ingested red cells show up the size of the amoeba which is more than 50 microns in diameter. The nucleus of the amoeba is partly masked by the red cells. (Mag. × 3,300).*

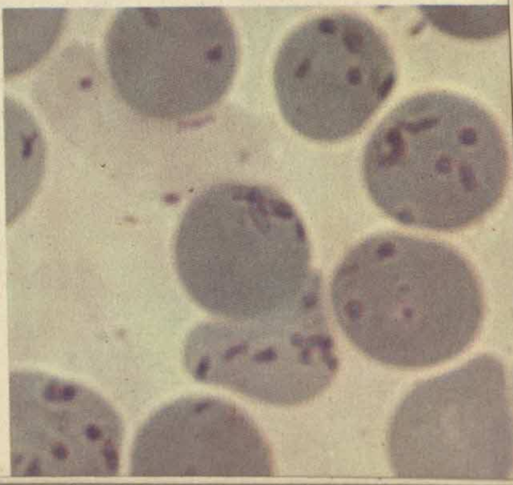
8. Trypanosomes in the blood: these are flagellate protozoa. The body is fusiform with an oval nucleus in the centre and a kinetoplast at the rear end. From here, a flagellum supports an undulating sheath along the length of the body, ending in a freely moving tip. Trypanosoma gambiense *and* T. rhodesiense, *trypanosomes from Africa, are the agents of sleeping sickness, transmitted by the tsetse fly* Glossina. *(Mag. × 5,500).*

9. Bartonella bacilliformis: *blood of a patient stained by Ronald Ross's thick-drop Giemsa technique; the parasites are highly concentrated; each spot is a* Bartonella. *(Mag. × 1,650).*





10. B. bacilliformis *in the blood of the same patient. This is an acute, often fatal, form of Peruvian bartonellosis, of which the chronic form is a verruca localized in the skin. The aetiological identity of these two clinical aspects was demonstrated by Carrien, a Peruvian doctor, who died of Oroya fever after inoculating himself with particles taken from a verruca. The parasite is inside the red blood-corpuscle, as is shown by the small light halo that surrounds it. (Mag. × 1,500).*



Malaria

Lucien C. BRUMPT

Most tropical diseases, whether caused by viruses, bacteria or parasites, require warmth as an essential factor for the development of these germs in their external environment or in intermediate hosts. Until recently, however, a certain number of such diseases existed in temperate countries; their decline is due partly to scientific progress and partly to economic and social improvements. Malaria is a characteristic example of this. How can the biological cycle of the parasite be interrupted in the human organism? How can communities and countries be protected against the harm it causes?

Malaria is still the most frequent infectious disease in the world. The number of people living in malarial regions is about three hundred million and the number of annual deaths from the disease is estimated at two million.

In the course of pre-history, the geographical distribution of human races was undoubtedly influenced by malaria, for not all races were equally susceptible to the parasite. Only naturally-resistant races, such as the Negroes of Africa and the Moïs inhabitants of Indo-China, have been able to survive in countries where malaria is hyperendemic and where more susceptible races would have been eliminated.

Malaria, at least, in its lethal form, which is caused by *Plasmodium falciparum*, has influenced most historical events, especially military campaigns. Today, it limits the agricultural and industrial development of numerous tropical countries where the question of manpower is all-important.

Malaria parasites are protozoa of the genus *Plasmodium*, found in red corpuscles of the blood during part of their complex development; this development includes an asexual cycle, *schizogony*[1] or Golgi's cycle, which takes place in man, and a sexual cycle, or *sporogony*, which takes place in a mosquito of the genus *Anopheles*, the exclusive role of which was demonstrated in India in 1879 by Ronald Ross and 1898 by Grassi, Bastianelli and Bignami. The erythrocyte-schizogony stage, known since its discovery by A. Laveran in 1880, is preceded by a pre-erythrocyte stage of schizogony, the development of which in the liver cells was described in detail by Short, Garnham, Covel and Shute in 1948.

Asexual cycle or schizogony

The sporozoite[2] inoculated by the bite of a female anopheline mosquito passes into the blood circulation, which it leaves after half an hour, and settles in the tissues. It is not immediately visible and because of this is called a cryptozoite. It becomes visible on the fourth day in a liver cell. At first, it is a cytoplasmic mass without any natural pigment, which increases in volume as the nuclei actively divide by schizogony; then each nucleus surrounds itself with cytoplasm and forms a merozoite. In the case of *Plasmodium vivax*, the agent of benign tertian fever,[3] one thousand are formed in ten days and forty thousand in seven days in the case of *Plasmodium falciparum*, the agent of malignant tertian fever. When the schizont[1] is ripe, the liver cell breaks down and liberates the merozoites, each of which penetrates a red blood corpuscle.

The young parasite, called a trophozoite, is capable of amoeboid movement and moves about inside the red cell, where it absorbs haemoglobin by osmosis. The trophozoite consists of a nucleus, cytoplasm, a vacuole and black granules of malarial pigment or haemozoin, the residue of haemoglobin digestion. When the nucleus divides, the parasite is

(1) Schizogony *(from Greek* schizein*—to divide, and* gone, *generation) : asexual multiplication taking place in the red cell and leading to the appearance of the* schizont, *after which the sexual cycle begins.*

(2) Sporozoite: *a parasitic form which results from the sexual cycle of sporozoa and constitutes the infesting form in mammals.*

(3) Tertian fever: *attacks of fever separated by recurrent one-day periods of no fever, which returns on the third day counting from the day of the preceding attack.*

called a schizont; the latter, on reaching maturity, looks like a rosette or daisy, with several merozoites arranged round a mass of malarial pigment. About eight merozoites are formed in seventy-two hours in quartan fever,[4] and eighteen in forty-eight hours in tertian fever. The rupture of the red host cells then occurs. This liberates the merozoites, each one of which penetrates into a new red cell and begins a fresh erythrocytic schizogony cycle.

The synchronized rupture of the red cells containing the ripe schizonts corresponds exactly with the beginning of the fever crisis, in which the patient passes through three stages: trembling, feeling hot, and sweating. The fever is thought to be due to the circulation of pyrogenic substances.

Clinical consequences

This schizont cycle suggests the following observations:

1. The destruction of a large number of red cells results in the appearance of several important malarial symptoms: anaemia, subclinical jaundice, and an increase of bilirubin in the blood and of urobilin in the urine, giving it a dark tint. Sometimes haemolysis[5] occurs very suddenly, started by cold or the absorption of quinine and causes an attack of haemoglobinuric bilious fever,[6] an extremely serious complication accompanied by renal disturbance.

2. No anti-malarial preparations, from quinine to the more recent synthetic products, act on the sporozoite or on the liver schizont, neither do they prevent invasion of the red cells; none of them is therefore truly preventive. These substances do not deserve to be called curative because they do not prevent relapses through re-infestation of the blood by tissue schizonts kept in reserve in the liver cells; they are merely suppressives, serving only to interrupt the schizogony in the erythrocytic stages. This is of the greatest importance, since schizonticide treatment will save the patient, provided it is begun in time.

3. Although erythrocytic schizogony has no apparent reason for stopping spontaneously, some patients recover without being treated, in spite of the fact that a number of anopheles may bite simultaneously and each may inject thousands of sporozoites at a time. In the case of *Plasmodium falciparum*, each sporozoite produces forty thousand merozoites in a liver cell in seven days; these invade as many red cells and multiply by eighteen every forty-eight hours. Even taking blood renewal into account, there should be no red cells left at the end of a few days, but the spontaneous recovery of a certain number of patients obliges us to accept the fact that there is a natural process of defence, the exact humoral or cytological mechanism of which has still to be discovered. The parasite, acting as an antigen, causes the formation of antibodies in the patient's serum—precipitins, agglutinins, lycins and, especially, opsonins. The latter activate phagocytosis. At the beginning of an attack on a new victim, the parasite causes non-specific phenomena of inflammation. Polynuclear neutrophils, normally microphages, are available in large numbers in the blood and in reserve in the bone marrow; facing the first assault waves of the parasites, they succeed in destroying about 60 per cent while waiting for the reticulo-endothelial system, which produces macrophages,[7] but is slower to start operating, and take over in the process of phagocytosis. This system includes mobile cells, such as the monocytes[8] in the blood circulation, and fixed elements, such as the Küpfer cells of the liver and those of the Billroth cords of the spleen. Hyperplasia of the reticulo-endothelial tissue of the spleen accounts for a symptom that is practically constant in malaria—splenic enlargement.

4. If the change in phagocytosis is missed out, schizont multiplication of the parasites is no longer balanced by their destruction and the intensity of the parasitaemia leads to a harmful attack of malaria. The red cells, parasitized by the ripe schizonts of *Plasmodium falciparum*, have a tendency to agglutinate and to line the walls of the capillaries, slowing down the blood flow and finally obstructing it. Thrombosis of the cerebral capillaries explains the predominance of neurological symptoms in acute malaria. The need to prevent vascular collapse makes it essential to combine anti-shock treatment with effective anti-parasite treatment, where the old-established quinine medication is still indicated.

The prognosis of these serious cases depends on emergency treatment based on early diagnosis.

When confronted with the occurrence of intermittent or continuous fever, sometimes observed in travellers, soldiers, pilots, hunters or fishermen returning from endemic-malaria zones, the possibility of malaria occurring in the tertian incubation period, ie, less than twelve days, must always be borne in mind.

Diagnosis can always be made by examination of the blood, particularly by using the Ronald Ross thick-drop test, since there is no malaria without parasites being in the blood.

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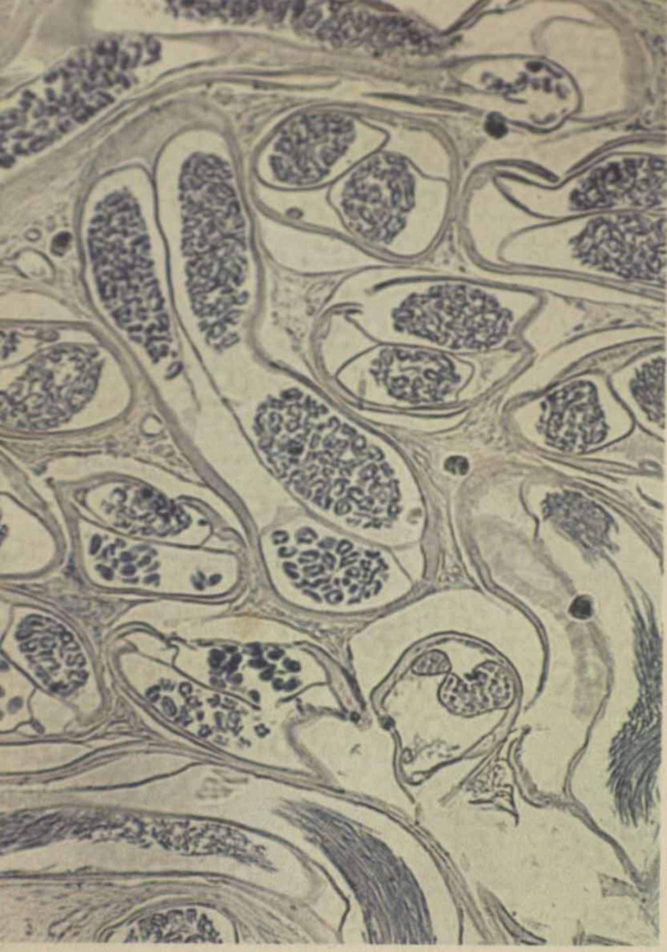
(4) Quartan fever: *attacks of fever separated by two days without it; fever returns on the fourth day, counting from the day of the preceding attack.*

(5) Haemolysis: *commonly called 'lacquering of red cells', from which haemoglobin is freed by destruction of its envelope or* stroma. *Haemolysis is either due to physical phenomena, such as hypotony of the fluid medium, or to the chemical action of enzymes, antibodies or lytic poisons, such as saponine.*

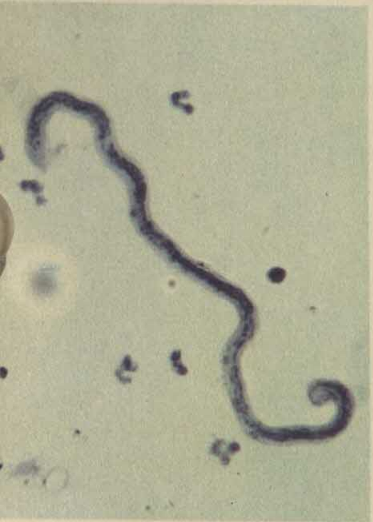
(6) Haemoglobinuria: *the presence of haemoglobin in solution in urine; to be distinguished from haematuria, where red cells are present in suspension in urine.*

(7) *In malaria, the stationary or mobile cells of the reticulo-endothelial system have the peculiarity of being filled with granules of brown pigment; this is not melanin, but haemozoin, or malarial pigment, carried in the cytoplasm. This pigment can be digested only by the macrophage cells of the reticulo-endothelial system, which specialize in the digestion of large particles.*

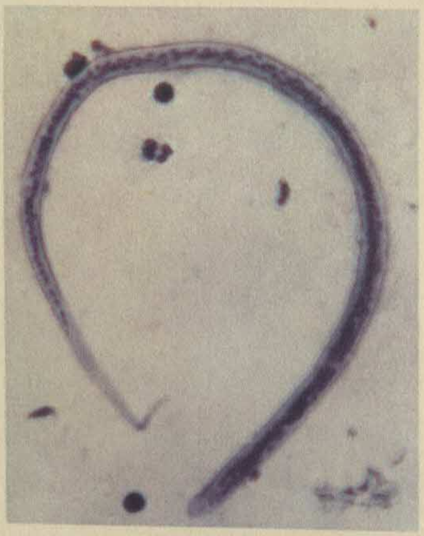
(8) Monocytes: *white cells (leucocytes) with a large notched nucleus.*



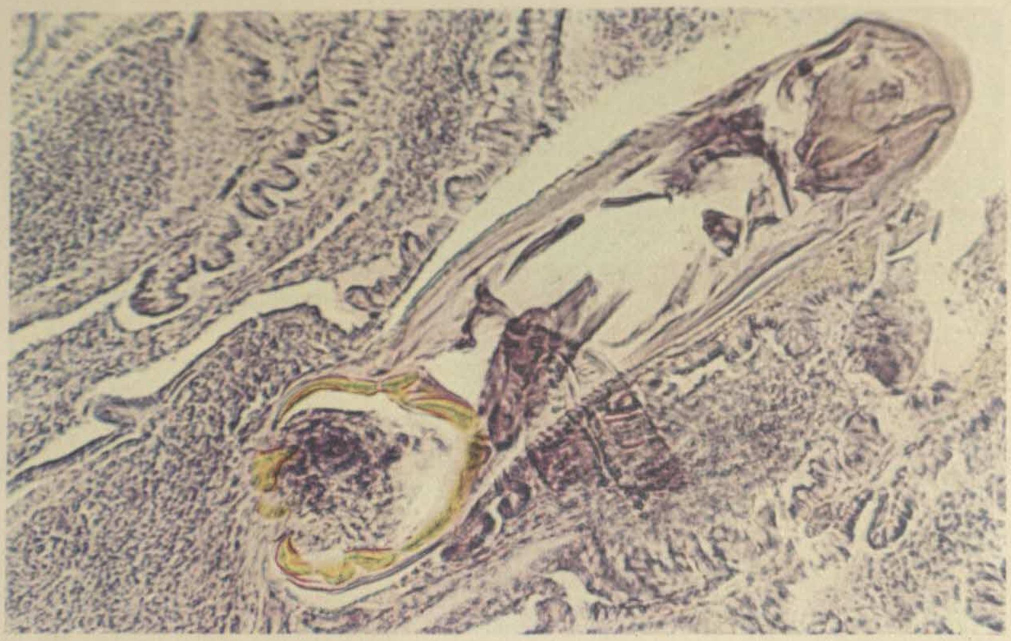
1. *Section of a fibrous tumour caused by* Onchocerca volvulus. *Onchocercae are filariae living in tumours of connective tissue; they are of the size of a hazel nut and are found under the skin, particularly where there is a bony support: the skull, around the shoulder blades, the ribs and ileac crests. The female filaria, 50 cm in length, is curled up and imprisoned in the fibrous tissue. Sections of the worm are shown at different stages, indicating embryonic maturation of embryos. At the top are shown bundles of microfilariae. (Mag. × 110).*



3. Loa Loa *microfilaria in the blood. It is 300 microns long and 8 microns wide. It shows in the blood only during the day; from there it is taken by a diurnal insect, the* Crysops. *It may be distinguished from Bancroft's microfilaria by its sinuous shape. Adult filariae or male and female microfilariae, 4 to 6 cm in length, live and move about in subcutaneous cellular tissue, causing allergic lesions known as Calabar swellings. This filariasis is to be found in tropical Africa. (Mag. ×500).*



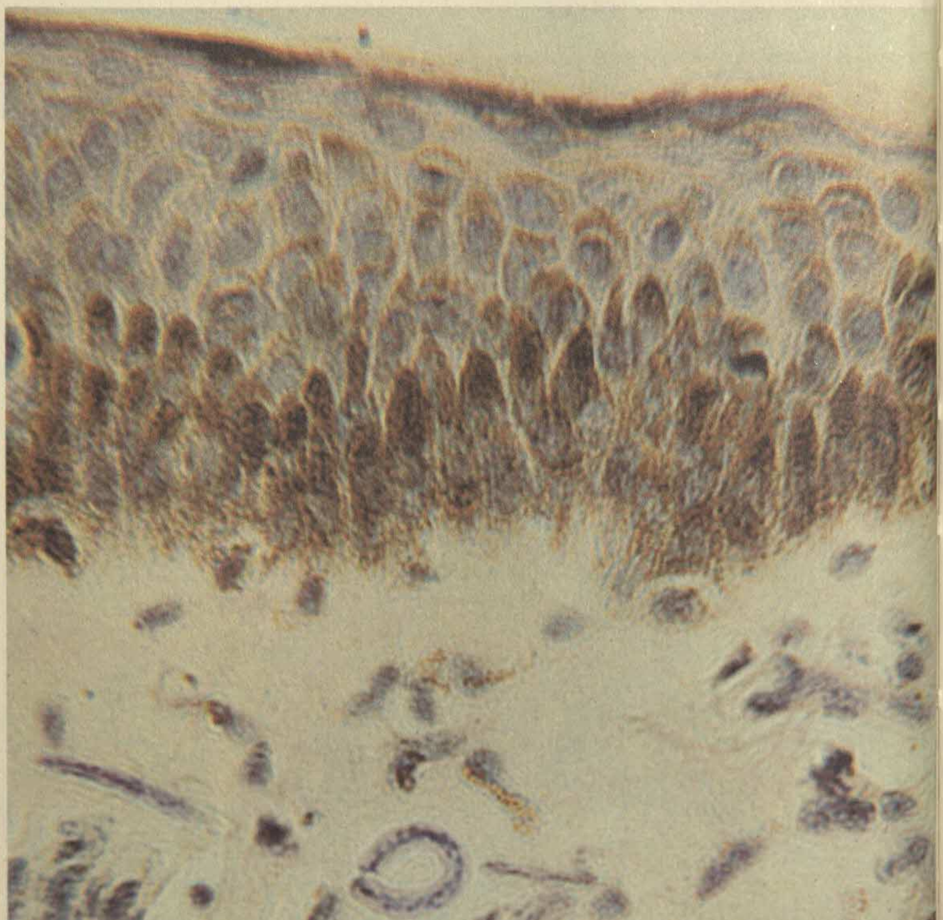
4. *Microfilaria of* Wuchereria bancrofti *in the blood. It is 300 microns long and 8 microns wide. Its external covering is easily seen; it is transmitted by* Culex fatigans, *a nocturnal mosquito, and may be distinguished from* Loa loa *by its open curved shape and smaller and clearly outlined somatic cells. The microfilariae live in the lymphatic system, accumulating above the lymph-nodes, causing stasis and swelling, lymphangitis, chyluria and, at a late stage, elephantiasis of the limbs or scrotum. (Mag. × 500. Photo Lod, taken at the Parasitology Laboratory of the Faculty of Medicine, Paris; slides prepared by Professors Gaillard and Brumpt).*



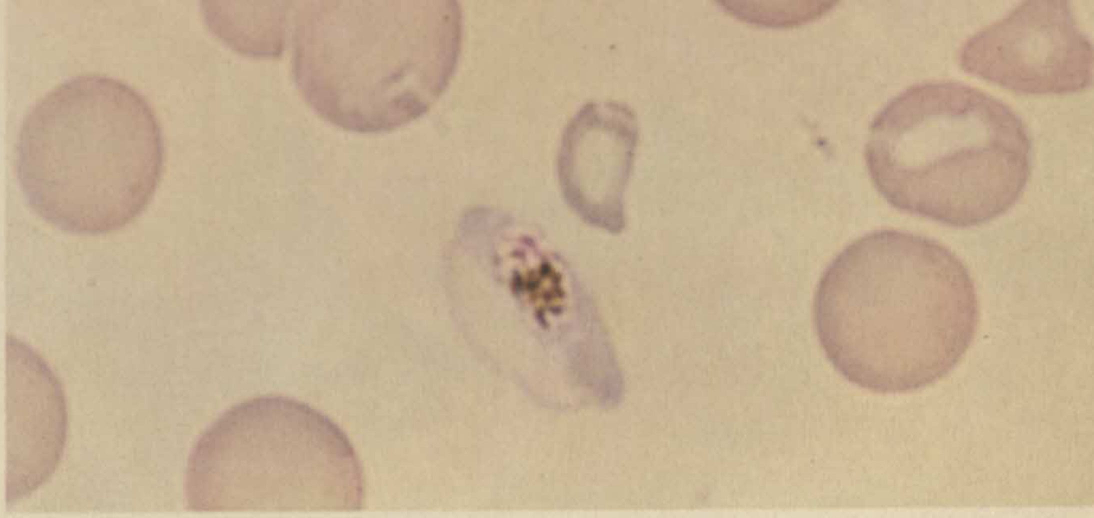
2. Ankylostoma, *the hookworm, a nematode, lives in the duodenum, attached by the hooks of its mouth to the mucosa from which it sucks blood. The amount of blood loss is 0·2 cc per worm per day. The hookworm causes miners' anaemia and tropical chlorosis. The blood loss caused by the worm is used in the treatment of haemochromatosis and bronze diabetes. (Mag. × 150).*

Diseases caused by nematodes

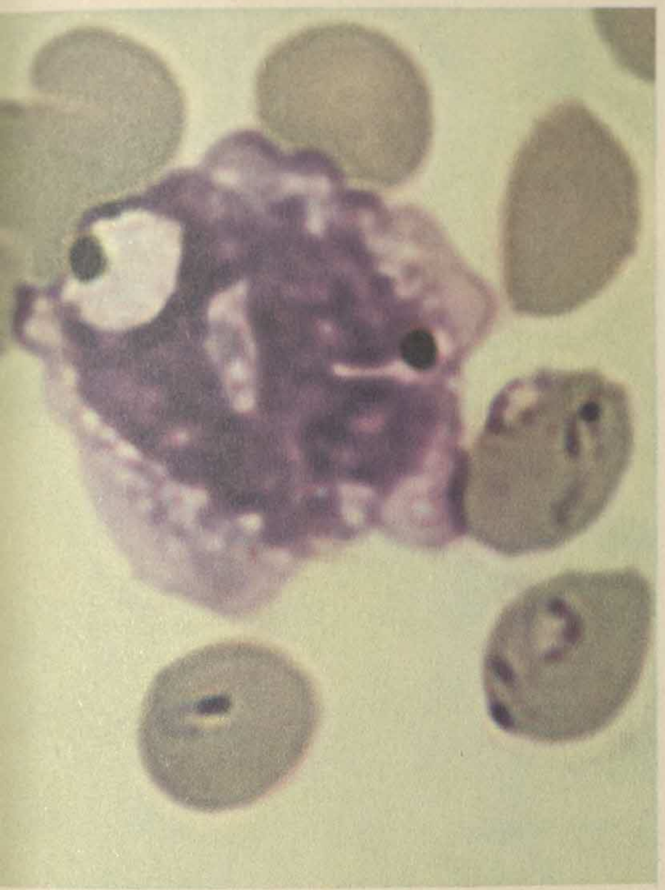
5. *Section of skin showing* Onchocerca volvulus. *These microfilariae, 300 microns in length, and without external covering, having been deposited in the connective tissue tumour, have approached the dermis by stages, sometimes going a long way from their point of departure. Here they are taken up by the vector insect, a* Simulium *or black fly. Some of the microfilariae will attack the eyes, causing ocular onchocerciasis, which may lead to blindness. (Mag. × 850).*



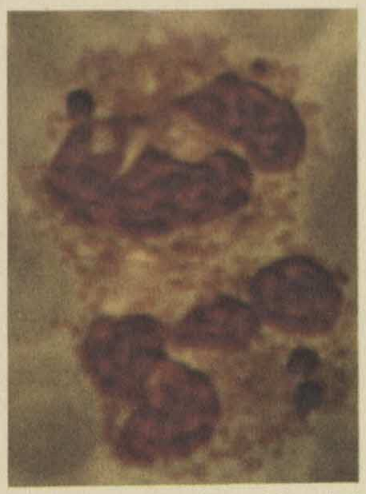
Malaria

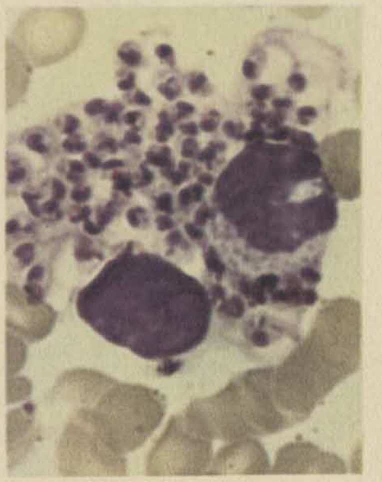


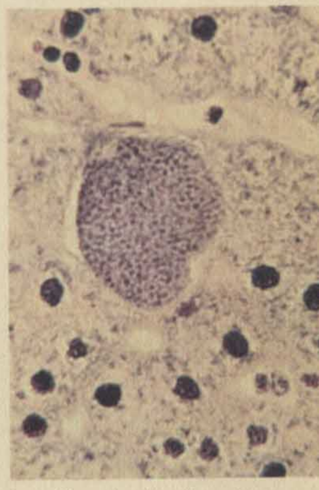
2. In the centre of the photograph, a female gametocyte of Plasmodium falciparum *(agent of malignant tertian fever), in the form of a crescent; in the centre, the nucleus, masked to some extent by malarial pigment. In the concavity of the gametocyte, the stroma of the host red cell, emptied of its haemoglobin, is still visible. These gametocytes appear during a malarial attack before it is treated and are the elements which will then infest the mosquito. The unequal sizes of red cells or anisocytosis and their deformations or poikylocytosis are evidence of malarial anaemia. (Mag. × 2,900).*



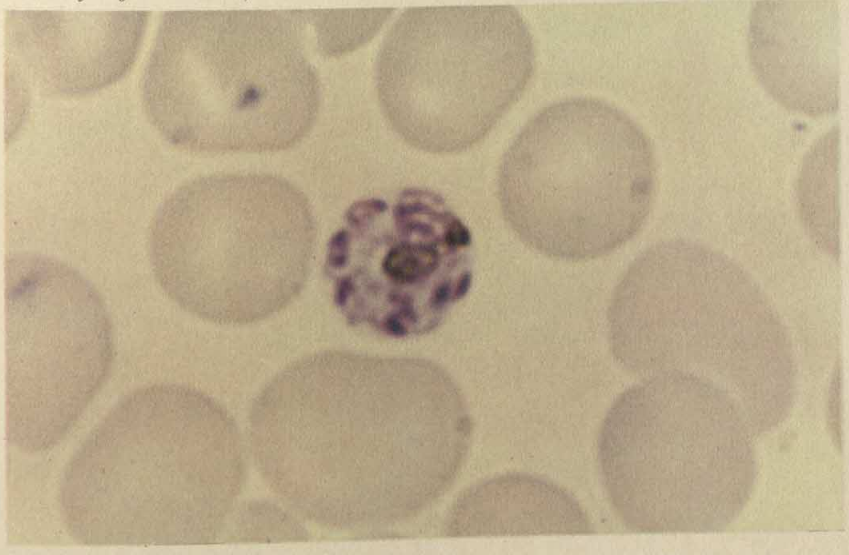
1. Monocyte containing malarial melanin. The monocyte, a mobile blood-cell, belongs to the reticulo-endothelial system, all components of which specialize in phagocytosis. This monocyte ignores red cells infested by young trophozoites and reserves itself for mature schizonts; intervening just before liberation of merozoites at rosette stage, the macrophage prevents the invasion of numerous red cells. (Mag. × 3,400). (Photos Lod, taken at the Parasitology Laboratory of the Faculty of Medicine, Paris. Preparations by Professor L. C. Brumpt, except photograph 5, which is by Professor Garnham).

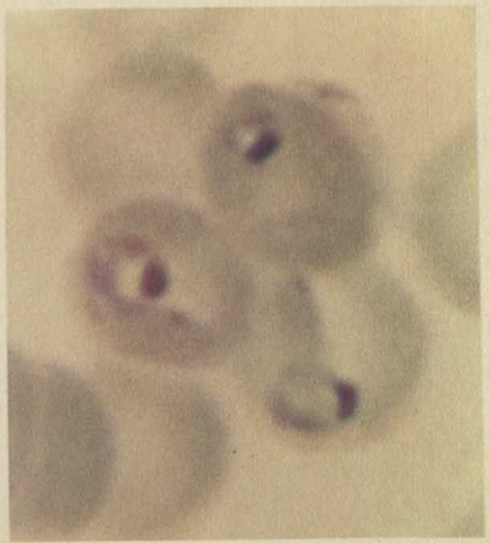


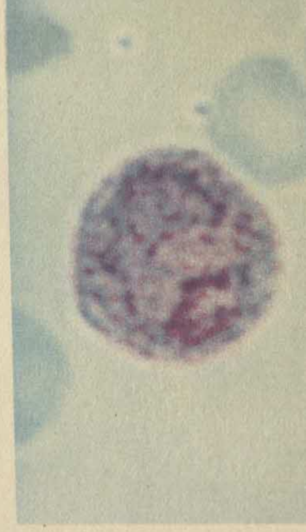




3. Polymorphonuclear cells containing melanin. One accumulation of malarial pigment in one and two in the other, correspond to phagocytosed groups of rosettes. (Mag. × 2,300). 4. Bone-marrow puncture in a case of visceral leishmaniasis. Leishmaniae are Flagellate protozoa, adapted to intracellular existence, and hence immobile; in the Phlebotomus, *the vector insect, they lengthen and become flagellated and mobile. The most typical leishmaniae are at the top and on the left, shaped like rugby footballs. The cytoplasm of the host-cell contains here about sixty leishmaniae. (Mag. × 1,400). 5. The sporozoite, inoculated by the mosquito, settles in a liver cell; it is transformed into a schizont living at the expense of the cytoplasm of the host-cell, of which it compresses the nucleus; here the ripe non-pigmented schizont is composed of thousands of merozoites which will invade the red cells to carry out the second phase of their cycle, erythrocyte schizogony.*







6. Ripe schizont of Plasmodium malariae, *agent of quartan fever: the small number of merozoites are placed round the mass of malarial pigment; these rosettes are observed just before the onset of malarial fever. The parasitized red cell is smaller than the normal red cells. (Mag. × 3,000).*

7. Trophozoite of Plasmodium falciparum, *agent of malignant tertian fever. This very small parasite is formed by annular cytoplasm (stained blue). The nucleus is situated on the cytoplasmic ring. The host-cell is identical in size and colouring with the healthy red cells. (Mag. × 3,000).*

8. Trophozoite of Plasmodium vivax *(benign tertian fever). The affected red cell is larger than the normal ones. (Mag. × 2,400).*

Early treatment does not always ensure recovery and malaria still claims its victims. For a long time, therefore, attention has been turned towards prevention of the disease, but for a proper understanding of methods of prophylaxis, it is essential to know the sexual cycle or sporogony of the parasite.

Sexual cycle or sporogony

The schizonts have already completed several cycles when parasites of different structure appear in the blood—the male and female gametocytes.[9] Those of *Plasmodium falciparum* are shaped like a sickle, which explains their name. These are incapable of continuing their development in man; removed by micro-manipulation and inoculated into another person, they do not give him malaria; it requires a few schizonts, or even a single one may suffice, to transmit the disease. This happens either voluntarily when benign tertian is used in pyretotherapy,[10] or accidentally in blood transfusion from malaria patients or drug addicts. Gametocytes can complete their development in the anopheles vector only when they are taken in during a meal of blood. In the hypotonic medium of the insect's stomach an emission of male gametes or flagella takes place, which go to fertilize the female gametes. After fertilization, the mobile egg moves towards the gastric wall of the mosquito, passes through it, and fixes itself under the external flap of this wall. This now stationary egg, the oöcyst,[11] is called a sporocyst which, after active nuclear division, leads to the formation of several thousand sporozoites. The bursting of the ripe sporocyst sets free the sporozoites; these then move towards the salivary glands of the mosquito, which they penetrate in order to settle in the salivary canals, ready to be inoculated when the mosquito bites.

The duration of sporogony in the mosquito varies with the species of *Plasmodium* and with temperature; it lasts on an average about two weeks. This completes the parasite's cycle.

The epidemiologist tries to interrupt the cycle either by preventing mosquito-borne infestation in a healthy person or by preventing the infestation of the mosquito by a gamete-carrying malarial person.

The prevention of malaria comprises two main courses of action: individual prophylaxis, which aims at protecting an uncontaminated person, and general prophylaxis, which consists in combating the reservoir of infecting agents, whether they are to be found in man or in the anopheles.

Individual prophylaxis

There are two means of protection from malaria: passive defence against mosquitoes, and chemoprophylaxis.

1. The ideal solution, of course, is to avoid mosquito bites. It is possible, knowing the flight range of anopheles, which varies according to species (over a mile, on the average), to avoid living too near ponds containing mosquito larva; to sleep under a mosquito net; and to withdraw at sunset into a house equipped with metal screens. The use of a protective screen aims at diverting the anopheles towards livestock stabled near the house. Also, camphor, citronella, or one of the many efficient substances used to repel insects, such as methylphthalate, may be applied to the skin.

As it is impossible to be certain of escaping mosquito bites, it is preferable to combine these measures with chemoprophylaxis. This should begin on the day of arrival in the malarial country and must be continued for two months after returning to a healthy country; the suppressive action of the drugs does not protect one from primary invasion,[12] or from relapses brought on by an air journey, by cold weather, or by a stay in mountainous country. Among the substances to use, chloroquine or nivaquine, which is an amino-4-quinoline, is well tolerated in daily doses and it has the additional advantage of being a prophylactic for amoebal hepatitis, a disease which is also frequent in tropical countries.

Chemoprophylaxis is very effective when applied in well-disciplined communities. Even in under-developed areas, mass prophylaxis can be made possible by the addition of chloroquine to kitchen salt.

General prophylaxis

Anopheles infestation must also be prevented, beginning with the parasite reservoir and continuing by actively combating the adult and larval anopheles.

Apart from some anthropoid apes which are sensitive to human *Plasmodium*, but of little epidemiological importance, the only carrier of the organism is man. The detection of malaria is based on searching for enlarged spleen, which gives information especially on endemic malaria,[13] and on searching for blood parasites, which give information on the epidemic aspect. Compulsory declaration of the disease is essential for judging the efficacy of anti-malarial measures. Isolation is unnecessary because malaria is not contagious.

(9) Gametocytes: *cells that produce the gametes, or male and female cells, the union of which will form the fertilized egg or zygote. Microgametocytes produce many male microgametes or flagella. Macrogametocytes give rise to a single female macrogamete.*

(10) Pyretotherapy: *a method of treatment which consists in causing artificial fever by various methods, such as the inoculation of malaria. It is used in the treatment of general paralysis.*

(11) Oöcyst: *a fertilized egg that reaches its maximum size (30 to 50 microns, according to the species of* Plasmodium) *before dividing.*

(12) *Delayed* primary invasion, *or* primary latency, *is sometimes observed with* Plasmodium vivax. *Though infected in the autumn, the victim has an attack of fever only in the following spring. In the case of* Plasmodium malariae *and* Plasmodium ovale, *these prolonged incubations can sometimes last many years.*

Early treatment of patients prevents the appearance of gametes. Once they appear, however, the gametes resist all the above-mentioned schizonticides; their destruction is obtained only by gametocide preparations of the amino-8-quinoline group. Unfortunately, these are fairly toxic and must be used with care.

Combating Anopheles

1. Measures against adult *Anopheles* have been radically transformed by the appearance of remanent insecticides. Their efficacy, however, does not do away with the need for very precise entomological study. There are about four hundred species of anopheles, of which only twenty are involved in the transmission of malaria; in each country, only one of the ten or fifteen local species needs to be combated. A precise knowledge of its biology results in a great saving in money and energy. The malariologist already has an idea of the pathogenic role of an anopheles, if there is a correlation between seasonal frequency of the insect and recrudescence of primary infections among, for example, infants less than a year old. The dissection of the stomach and salivary glands of mosquitoes caught indoors or out of doors enables one to find the oöcyst and sporozoite indices for each species. These statistics are sometimes very different from those obtained experimentally from laboratory mosquitoes fed on gametocyte carriers.

Parasitic efficacy, or the ability to transmit malaria, has epidemiological consequences only if the biology of the anopheles places it into contact with man. Two factors are important; habitat and feeding habits. Certain wild mosquitoes inflict bites out of doors; domestic species feed and shelter indoors. Analysis by means of precipitating serums of the infested haemoglobin shows whether the origin is human or animal. It is easy to understand that anopheles that are both domestic and feeders on man are the most dangerous vectors.

Remanent chlorate insecticides, DDT, or dichlorodiphenyl-trichlorethane, HCH, or hexa-chloro-cyclo-hexane and its isomer, gammexane, chlordane and dieldrin, act by contact, by being dissolved in the lipoids of the insect cuticle, whence they penetrate the nervous system. It is sufficient to apply DDT to the walls of a house twice a year, allowing about two grams per square yard. Remarkable success has been achieved in Venezuela, where *Anopheles darlingi* is a feeder both on man and domestic animals. Elsewhere, however, cases of natural or acquired resistance have appeared which have necessitated a search for new insecticides, particularly among phosphoric esters dangerous to man and domestic animals. Some *Anopheles* modify their biology in order to escape the insecticide; in the United States, *Anopheles albimanus* bites its victims indoors and digests out of doors; faced with DDT, *Anopheles gambiae* in Africa has turned wild, although remaining a feeder on man.

2. Before remanent insecticides were used, the first aim of prevention was to combat larvae; even today, this is still useful. Anopheles larvae on the whole prefer small sunlit ponds containing clean but stagnant water, although many dangerous species, eg, *Anopheles minimus*, the most dangerous malaria vector in Indo-China, look for gently running water.

Anti-larval measures may be carried out by filling in swamps, covering over, draining and pumping. These large-scale measures are three times more expensive than those used against adult mosquitoes; they are, however, justified in the neighbourhood of large towns, where potential building sites or valuable agricultural areas can be reclaimed and there is a labour force sufficient to exploit the reclaimed land.

But these conditions are not always to be found together, and it is possible to employ more economic small-scale measures of reclamation of a mechanical, chemical and biological nature. Among these are anti-erosion works on river banks, clearance of ponds, and the diversion of water-courses. Chemical substances, such as petroleum, kill larvae by asphyxia, or by ingestion, as with Paris green (aceto-arsenate of copper), or by contact with chlorated insecticides of the sort used against adult mosquitoes. A knowledge of the biology of each species indicates the measures which must be taken to combat the pest, eg, by preventing sunlight from reaching the ponds of *Anopheles gambiae*, which need light, or by the suppression of vegetation around the ponds of *Anopheles umbrosus*. Dirty water kills anopheles but favours *Culex* and *Aedes*. Finally, we must not forget the *Gambusia*, a viviparous fish that eats mosquitoes. This is a useful aid, involving little cost.

The prophylaxis of malaria, a disease of under-developed countries, requires financial measures that can be supplied only by the state or by international organizations; it also requires the co-operation of the populations, a reliable health organization, and an efficient administrative authority.

(13) Endemic and epidemic *areas: an endemic area is one where sporadic cases, few in number, appear during the year and every year. An epidemic is observed in a non-immune population as a simultaneous and unexpected appearance of numerous cases, with either seasonal predominance or multi-annual recrudescence.*

Hypersensitivity

Raoul KOURILSKY

Hypersensitivity reactions very often occur when external factors have started biological mechanisms within the body. The most frequently found hypersensitivity complaint connected with particle inhalation is asthma, one of the least well understood and least efficaciously treated of such disorders. Asthma is strongly affected by the nervous system and by the psychological state of the patient. Provided that these essential factors are taken into account, complete recovery is possible.

The definition of a hypersensitive person, ill or well, is that of someone who reacts to substances that are harmless to others. He may also respond in an exaggerated manner to certain substances in amounts which others would tolerate, or may be sensitive to a much smaller amount of it than a normal person would be. This reaction does not depend on pharmacological properties of the substances concerned, but on a special condition of hypersensitivity to a substance.

Serious and possibly fatal consequences may arise if the functions that control the physiological condition of the body and maintain *homeostasis*[1] (the state of equilibrium in the body) are markedly upset.

Accidents and illnesses caused by hypersensitivity have become known through observation on human beings, but the way in which many of the mechanisms work that result in hypersensitivity have been discovered mainly through experiments on animals.

Protection of the internal environment of the body

Hypersensitivity is connected with the penetration of foreign substances into the body. As Claude Bernard pointed out, the stability of the 'internal environment' is the essential condition for the life of body cells which in this way receive all the necessary substances and energy requirements in the same proportions. Among the regulating functions that ensure this 'physiological autonomy', there are those that rid the body of those foreign substances that penetrate into it. These foreign substances consist of proteins, large molecules of a molecular weight varying between 130,000 and 160,000, made up of smaller amino acid molecules, each with a molecular weight of approximately 5,000 arranged in a definite pattern.

A large number of these proteins are derived from foods. These are gradually broken down by enzymes secreted by glands dotted along the digestive tract; the final products then pass through the liver, where they are broken down into small amino acid molecules.

All living cells, including liver cells, use these small molecules, building them up into new molecules of a weight, size and spatial arrangement conforming exactly to those already possessed by that particular organism. This synthesis is controlled by the action of

(1) Homeostasis: *see 'Correlations between Organs' by Pierre Vendryès, page 155, Volume 5.*

(2) *In this way each organism maintains its own specificity linked to the particular spatial configuration of protein molecules.*

genes, particles of deoxyribonucleic acid in the chromosomes of every cell nucleus which determine the formation of the enzymes required for molecular synthesis[2] in the cytoplasm.

However, if these large molecules penetrate directly into the internal environment, organ and tissue cells cannot incorporate them and the body has to get rid of them in another way. This is done by (1) removal of these extraneous molecules, (2) their transformation by physico-chemical means.

Removal from the internal environment

The reticulo-endothelial system, consisting of special cells dispersed throughout nearly all the tissues and organs, is concerned with the removal of foreign particles from the body, whether these particles are inert or inactive, mineral or organic. Whatever their composition, the foreign particles are captured by special phagocyte cells. These cells are found on the inside walls of capillary vessels (endothelial cells) and in all filling and supporting connective tissue (histiocytes), whether under the skin, in the mucosa, or in the spaces between organs.

There are also special areas where the number of these cells is very large and where they are very active. They are abundant in those organs that filter large quantities of blood or lymph; for instance, the liver (Kupffer's cells), the spleen and bone marrow, which is in direct contact with venous circulation, and the lymph nodes, which represent staging centres along the lymph ducts that remove a series of substances derived from the tissues.

Physico-chemical transformation

Physical and chemical transformation is the task of special cells, some of which belong to the reticulo-endothelial system. One group, made up of circulating polymorphonuclear cells and tissue phagocytes (histiocytes) disintegrate large molecules into their constituent amino acids. Another group, belonging to the series of white blood cells, specialize in protein synthesis: plasmocytes and probably lymphocytes. Remarkably enough, these cells synthesize a globulin that is a mirror-image molecular replica of the initial substance, made on an intra-cellular template. This mechanism, once started, can remain active for months, or even years. The replicas remain hidden in the cells, but in the majority of cases will spread into the general circulation after eight or ten days in a sufficient quantity for them to be detected.

They are called *antibodies* because they have the property, when they find the initial substance, called an *antigen*, of becoming affixed to it and of starting a series of reactions that vary according to the nature of the antibodies and their position in the tissues.

This mechanism is a general phenomenon and constitutes one of the essential physiological methods for the defence of the body (immunity). Antibodies formed against bacterial proteins provide an obstacle to bacterial activity; for instance, they neutralize toxins and agglutinate, precipitate, or disintegrate bacteria. Other reactions, however, may occur. These can be harmful to the body and they come under the heading of hypersensitivity.

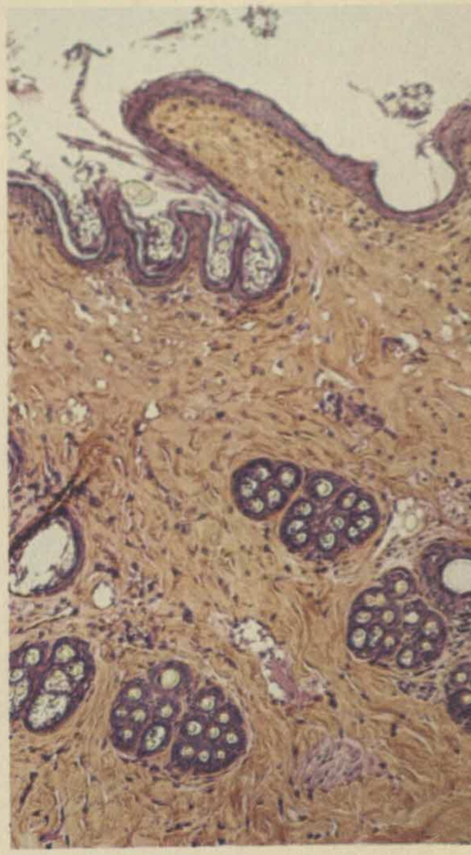
The reaction between antigen and antibody may be produced inside the phagocyte cells containing antibodies. This can cause marked enzyme disturbance in these cells. Disintegration follows from this, liberating highly toxic products into the tissues which react locally, thereby affecting the circulation, coagulation, vascular permeability, smooth muscle, etc.

Wherever an antigen encounters an antibody, signs of oedema or of inflammation will therefore occur: if these reactions become general, they may lead to death, due to disturbances of the vital functions of respiration, circulation, and nervous activity.

The appearance of hypersensitivity

If any protein substances (antigens) are introduced into the body, except through the digestive tract, antibodies will be produced and the conditions for an antigen-antibody reaction conducive to hypersensitivity will be fulfilled and the body will become sensitized. Further introduction of the same foreign substance will trigger off the antigen-antibody reaction. The intensity of these reactions varies considerably from one person to another, because the degree of sensitization is very unequal and because the controlling functions, especially of the nervous system, are very varied in different people. It is not yet known what all these conditions are, but once a person is sensitized, he is likely to be affected each time the antigen is encountered.

Most substances used in medical treatment are of protein nature: antitoxic sera prepared from horse serum, hormones, organ



Skin inflammation, caused by hypersensitivity. At the top of the photograph, the epidermis (the darker border); below this, the superficial dermis, then the deep dermis, showing the cells. The deep dermis shows slight oedema between the sebaceous glands and the base of a hair. Two connective fibres are shown, stained blue. (Photo Lod).

I EXTERNAL ALLERGENS

(a) especially dust allergens

- House dust

BEDDING ALLERGENS
- Feathers, especially
- also, wool, kapok and horse-hair

ANIMAL FUR
- Cats
- Dogs
- also rabbits and cattle

MOULDS
- There are numerous species, but more especially:
- Alternaria
- Cladosporium
- Mucor
- Rhizopus
- And to some extent:
- Aspergillus
- Penicillium
- Botrytis
- Stemphylium
- Neurospora

POLLENS (These cause asthma only in association with hay fever). They include especially the graminaceae:
- Phleole, Dactyle
- also,
- Plantain, Rumex
- Parietaria
- Composites (Artemesia)
- Trees (lime, plane, chestnut, etc)

OCCUPATIONAL ALLERGENS
- Cotton fibre, castor-oil seed
- Gum arabic (printers)
- Flour (bakers)
- Ipecacuanha (pharmacists)
- Antibiotics (specialized factories)

(b) different food allergens

- Flour
- Milk
- Potatoes
- Citrus fruits, etc.

I INTERNAL ALLERGENS (saprophyte or virulent infection)

microbes

- Streptococci
- Staphylococci

ungi

- Candida albicans (highly important)
- Epydermophyton
- Trichophyton

and tissue extracts and antibiotics (mycelium extracts). These have to be handled with great circumspection and with a sound knowledge of the sensitization conditions involved. Although the most dangerous substances are nitrogenous compounds of high molecular weight, they are not the only ones capable of inducing sensitization; polysaccharides, large molecules of carbon, hydrogen and oxygen, behave in the same way. It is known also, from the work of Landsteiner, that even simple chemical substances (such as pycryl chloride and dinitro-chlorobenzene) may combine with the proteins of the organism to cause antibody production and create hypersensitivity to these chemicals, which are called haptens.

The human organism is thus not protected from hypersensitivity produced by simple organic or chemical substances (such as aspirin and pyramidone), which up to now have been considered relatively inoffensive because they are not made of protein and because they are administered by mouth. Fortunately, hypersensitivity reactions do not always occur. For a reaction to take place, a precise proportion must exist between the amount of antigen and antibody. According to whether there is an excess of one or the other, hypersensitivity will or will not occur. Many factors are concerned in the production of these quantitative relationships. The amount of antigen in the body depends on the frequency, repetition, duration, and rhythm of its introduction. The quantity of antibody depends on the speed of its synthesis and on the number of its templates. This varies with the individual; there are strong and weak producers of antibodies. This is a genetic character, but the rhythm and manner of exposure to the antigen are very important factors.

Hypersensitivity may be classified into two groups: immediate and delayed.

Immediate hypersensitivity

This form of hypersensitivity is linked with the presence of *circulating* antibodies, which may be transferred to a healthy organism by the injection of blood serum containing antibodies either into the veins (in the guinea-pig) or under the skin (in man). When this *passive transfer* has been effected and the antigen is injected into the organism that has received the serum (whether in the general circulation, as in the guinea-pig, or in the centre of the injection area, as in man) characteristic symptoms appear. This method is currently used to determine whether a person is sensitive to a given antigen.

Anaphylactic shock

Hypersensitivity of the *anaphylactic* kind is the prototype of immediate sensitivity. In fact, the terms are synonymous. This type of sensitivity is linked with the circulation of thermostable antibodies. It is released when the antibodies are in the presence of an excess of antigen. The most dramatic case, anaphylactic shock, discovered in 1902, by Richet and Portier, in the dog, was observed in man after repeated injections of horse antitoxin serum used in the treatment of infectious diseases.

The sensitization created by a single previous injection varies according to species. Sometimes an infinitesimally small dose suffices (for instance, 1 microgram of ovalbumin or one millionth of 1 cc of horse serum).

After eight to ten days, antibodies are present in the globulin fraction of the plasma. Even if only a small quantity of antigen is injected under the skin, the concentration of free antigen in the organism may be fifty times stronger than the circulating antibodies. An excess of antigen is then present, the effect of which is to cause a terrifying shock that is often fatal within a few minutes. Symptoms vary in each species.

What has happened is that the antigen-antibody reaction releases the action of a ferment (protease) which disintegrates intracellular proteins and frees a series of chemical substances—*histamine* (imidazol-ethylamine), acetylcholine, serotonin (5-hydroxytryptamine), bradykinine, hyaluronidase, and many others.

Histamine is the most important of these substances. Sir Henry Dale has shown that histamine causes a contraction of smooth muscle of the intestine, uterus, and lungs, both *in vitro* and *in vivo*. Its action may be suppressed by anti-histamine substances, and this has been the object of some remarkable studies by Bernard Halpern. They protect both animals and man from the effects of shock.

The Arthus phenomenon

When repeated injections are carried out with soluble protein substances capable of causing shock, a high production of circulating antibodies (Rich and Gregory), and a large local excess of antigen occur. Very intense local inflammatory symptoms are then produced, which are known as the Arthus phenomenon (1903). They are characterized by considerable oedema, extravazation of blood, invasion of polymorphonuclear leucocytes, and secondary necrosis. Antihistamines are not effective (Ovary and Bier). Repeated local injections of therapeutic serum in the same place should therefore not be given.

A highly specific disease observed in man, which is nearly always fatal, is *periarteritis nodosa* which is probably linked with this type of sensitization. Unfortunately, it is difficult to detect the antigen responsible, the initial introduction of which may go back for years and coincide with the introduction of numerous other antigenic substances.

A particular variety of immediate hypersensitivity was described in 1933 by Coca as *atopic* hypersensitivity (from a Greek word meaning 'strange, abnormal'). The symptoms, which are purely transitory, are rapid appearance of oedema, urticaria and reddening of the skin, following the introduction of certain substances. These symptoms are linked with circulating antibodies. They may be reproduced in a healthy person by a local injection of the antigen into an area of skin injected the day before with serum from a sensitized person (passive transfer[3]).

Delayed hypersensitivity

The notable difference between delayed and immediate hypersensitivity is that in the delayed form if a sensitized person is re-injected with the same antigen, the symptoms do not appear at once, but only after a certain interval of time (from a few hours to twenty-four hours). The main symptom invariably consists of local inflammation, which reaches a maximum in forty-eight hours and then slowly disappears during the next two or three days. If the reaction is strong, the inflammation will be necrotic at the centre.

This reaction was described in 1907 by von Pirket, who had observed it in tuberculous patients who had been injected with tuberculin. This was called 'allergic reaction', and was the prototype for all later discoveries of bacterial and mycelial allergies. The same reaction is also to be found in coccal infections (pneumococci, streptococci, and staphylococci), in diphtheria, whooping cough, brucelloses, syphilis, and virus infections, as well as in mumps, influenza, scarlet fever, and herpes. All mycoses fungus diseases cause this reaction. The number of these disorders continues to grow and greatly exceeds diseases caused by pathogenic agents.[4]

The intolerance observed after treatment with most medical preparations (cutaneous eruptions, pruritis, and fever) is caused by delayed hypersensitivity. Such phenomena are to be found in very diverse circumstances, as, for example, in treatment with novarsenobenzol (for syphilis), with barbiturates, some alkaloids (especially quinine) and even ordinary aspirin, antipirine, and salicylic acid.

Disorders produced by tissue disintegration (brain, cornea, and testis), encephalomyelitis, cataract, or aspermatogenesis (auto-antibody diseases), are accompanied by delayed sensitivity.

The rejection of grafts in subjects of the same species occurs when the receiver of the graft is in a condition of delayed hypersensitivity to the antigens contained in the donor's graft.

Although the importance of delayed hypersensitivity is constantly increasing, the mechanism involved is not nearly as well understood as that of immediate hypersensitivity. It is known, however, that there are no circulating antibodies, but that the cells have acquired certain special properties. It is possible to transfer delayed hypersensitivity to a healthy organism by injecting not serum, as in the case of immediate hypersensitivity, but cells from lymph nodes, blood, or peritoneal fluid, resulting from aseptic irritation.

In man, contrary to observations made with animals, transmitted sensitivity may last a long time, perhaps even for several months, despite the very small quantity of injected cells—120,000 to 130,000 per cc, a total of 2 to 3 cc in all (Sherwood Lawrence).

The existence of a reaction between antigen and a substance present in the cells has been shown by Rich in tissue culture. Following the addition of the antigen, cell growth and migration are inhibited. In the body organism this reaction causes inflammation, though this is not due to the liberation of substances, in particular histamine, the role of which has been demonstrated in immediate sensitivity. Antihistamines, therefore, have no effect. Only hormones from the suprarenal cortex diminish the reaction because they bring about a generalized diminution of the number of cells involved in the inflammation.

Relations between the two types of hypersensitivity

As research immunology extends, it is becoming clear that the different types of hypersensitivity overlap. Dienes and numerous others have confirmed that after an injection of antigen (serum albumin or oralbumin), there is a delayed transitory hypersensitivity phase which occurs before the

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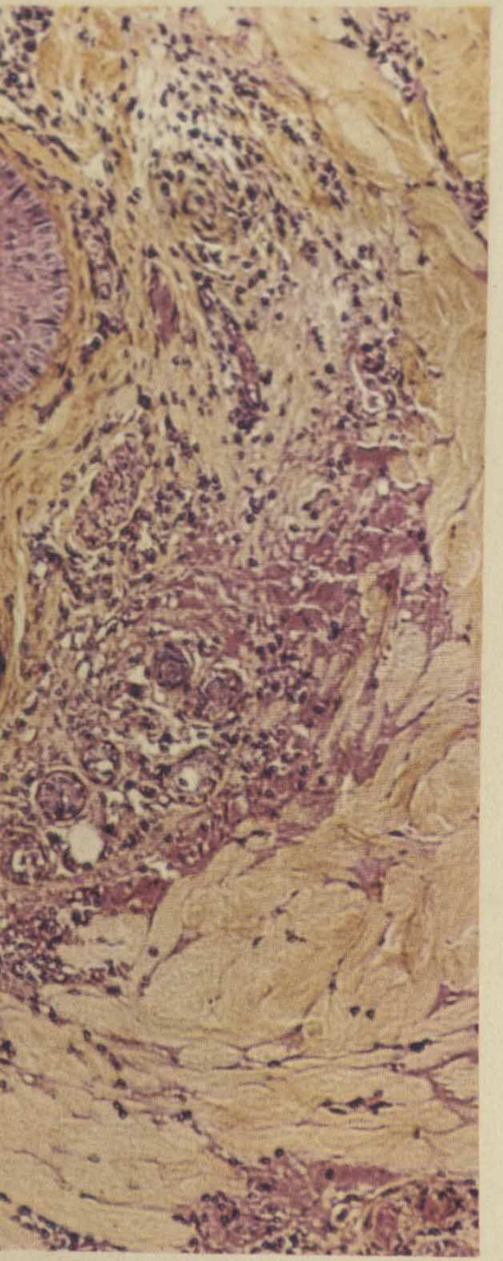
(3) *Antibodies, called 'reagins' are not thermostable, as are anaphylactic antibodies; they sensitize only the skin and are destroyed by heat. This kind of hypersensitivity is extremely frequent: urticaria, swollen lips and face, as well as asthma, are among its typical manifestations.*

(4) *Dermatitis caused by repeated contact with simple or organic chemicals is linked with delayed hypersensitivity. It occurs, for instance, in chemists and nurses handling antibiotics.*

Cellular reactions obtained after the injection of sensitizing substance in subcutaneous tissue. At the edge of the photograph, a sebaceous follicle with, in the centre, mobilized inflammatory cells of local or circulatory origin. (Photo Lod).



appearance of circulating antibodies on the tenth day.

In numerous pathological cases, it is possible to detect circulating antigens, and, at the same time, signs of delayed hypersensitivity from hypodermic reaction. The prototype of such conditions is *serum sickness*, described in 1905 by von Pirket and Schick. This begins eight to ten days after injection of horse serum, at the same time as the appearance of circulating antibodies. It lasts for some weeks and is accompanied by pains in the joints, skin eruptions, and waves of fever, although by then it can no longer be classed as immediate hypersensitivity.

Counteracting effects of hypersensitivity

The problem arises only in cases of immediate hypersensitivity. Preventive action must, above all, be taken because it is the repeated injection of a substance that causes trouble. No time lapse, for instance, should be allowed between horse-serum injections, because after a certain interval of time, there is a notable risk. Serum treatment should be continuous, not intermittent, nor should it be resumed after a lapse of ten days. If it should become necessary to give a serum injection after a prolonged interval, the patient must be desensitized by periodic injections at close intervals, of three to four doses of 0·1 to 1 cc, within one hour (Besredka's ceptophylaxis).

Antihistamines are of great value in all cases where the liberation of histamine has been demonstrated (anaphylaxis and atopia): in other cases they are of no use.

Suprarenal cortex hormones strongly diminish any hypersensitivity reactions, but their action is palliative and they can only be used within a certain interval of time, failing which serious complications may occur, such as metabolic disorders and secondary infections.

Hypersensitivity forms a chapter in the history of medicine which is being completely re-written. The amount of work and research dedicated to the subject in the last ten years is considerable and is still growing. The more the problem is explored, the more the fundamental processes of life are revealed—the renewal of the substance of the body, its genetic constitution, the regulation of its molecular composition and of its cellular enzymes.

It would be difficult to exaggerate the practical importance of hypersensitivity, knowledge of which is essential in all chemical and biological treatment in order to prevent accidents that might be caused by the use of drugs. Reaction risks increase with the rate at which complex and highly active chemical substances are brought into use.

Both patients and doctors should understand that you cannot introduce into the internal environment any given substance at any time and in any manner merely because certain symptoms have appeared.

Asthma and allergens

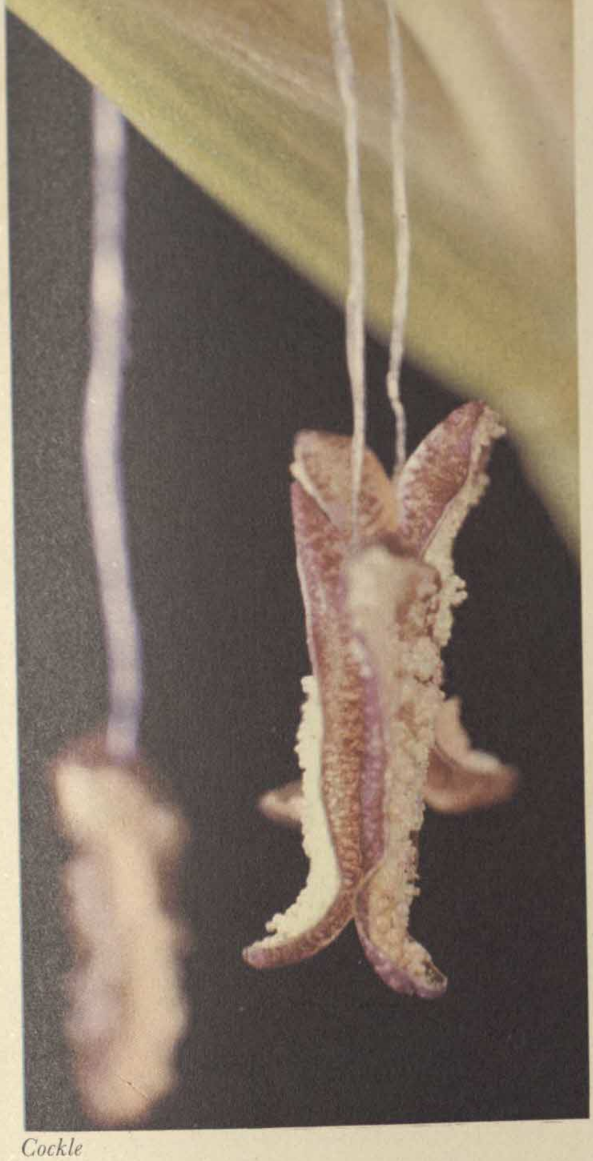
Although asthma is a widespread disorder it is not well understood and is badly treated. The symptoms have always been known and both doctors and patients have long realized that asthma is a condition rather than a disease, which may appear at any age. It may recur after long or short periods, or intermittently at protracted intervals; sometimes it may appear only once, but in other cases it occurs day after day with such serious effects that the patient hovers between life and death. Or it may be continuous and so mild that it occurs only when the patient makes an effort or climbs stairs, as with heart-disease.

In babies, asthma occurs as a crisis of febrile bronchitis, simulating an accidental respiratory infection. Eczema and skin eruptions (prurigo) show the existence of hypersensitivity to milk or milk products.

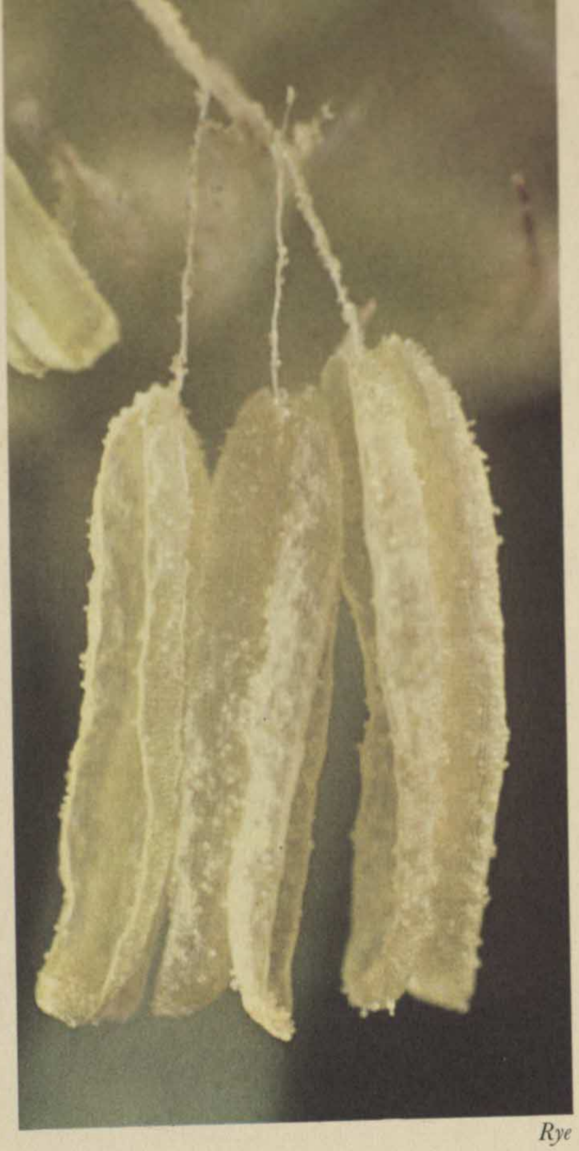
In older children, asthma appears also as periodical winter bronchitis or repeated attacks of infectious bronchial catarrh, although the intensity of the crisis may be revealing. From five to six years skin hypersensitivity

(1) Oedema: *swelling of tissues with interstitial fluids.*

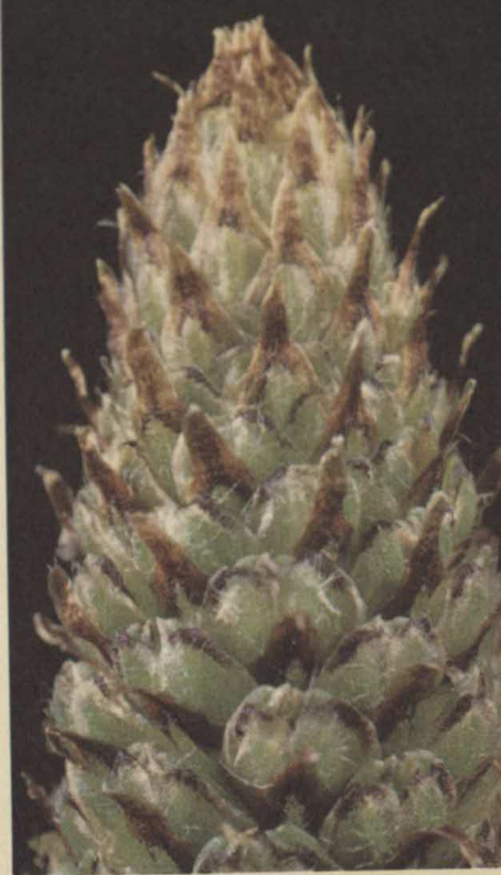
(2) Polymorphonuclear cells: *white cells with helical nuclei containing chemically different granulations. They are normally in the circulation and in inflamed tissues.*



Cockle

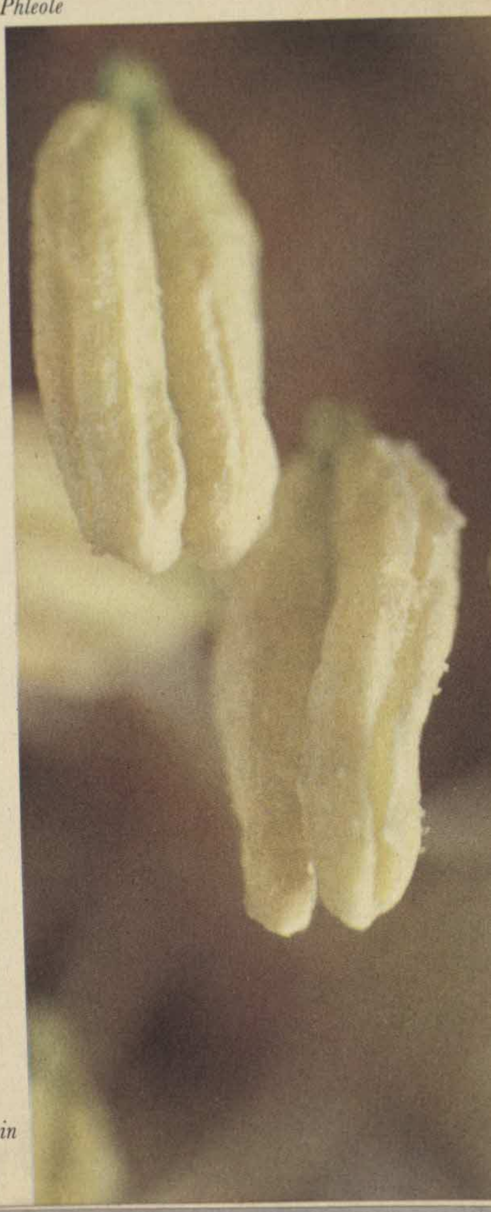


Rye

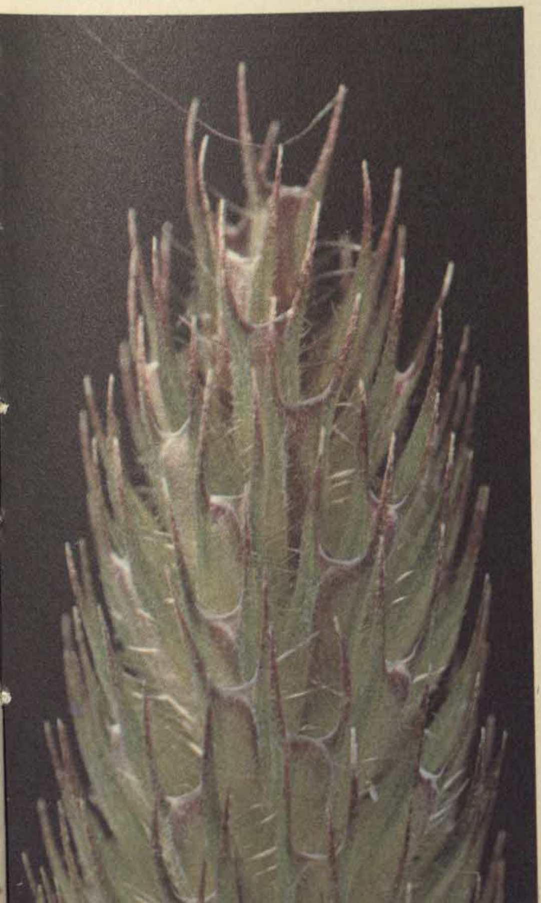


Phleole

Allergens are the cause of such common ailments as asthma and hay fever, and are antigens of a particular kind, provoking a respiratory or skin hypersensitivity reaction. The pollens of certain plants are a characteristic example. (Photo Lod, from the Pasteur Institute, Paris, by permission of Dr Guibert).



Plantain



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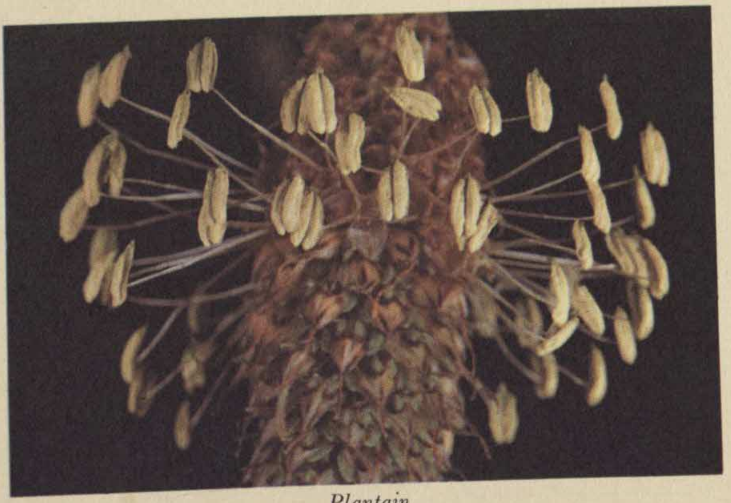


Plantain

Plantain pollen (Plantago lanceolata) *responsible for certain forms of asthma (Photo Pasteur Institute, Paris, by permission of Dr Guibert).*

is often detected. Infection of the lungs by normally harmless bacteria is frequent and asthma may be concealed by bronchitis. There may be many other masking symptoms: angina, tonsilitis, sinus infection, chronic colds, coryzas, accidental virus or bacterial infection, most often from streptococci.

In adolescents, asthma appears independently of any infection. There is no distinction between the sexes and in spite of what has been claimed, any connection with puberty is purely chronological.

Asthma is a disturbance characterized by difficulty in breathing out. It is always accompanied by bronchial irritation, shown by coughing and, after the crisis, by a particular kind of expectoration. It is frothy or thick, and consequently difficult to get rid of. When it eases, the crisis stops. The sputum is not purulent, unless it is infected, and there is no fever.

Crises may occur during the day or at night, and usually there is no clear-cut cause. Damp in the atmosphere or in the environment, or suspended dust or smoke may precipitate a crisis in some people, and, as with many other conditions, menstruation may exaggerate an attack. But the explanation of the repetition of asthma crises is never absolutely clear.

In adults of both sexes, asthma may occur at any moment for no apparent reason. Associated infection may also appear (though much less often than in children) and when this infection does take place the patient has the greatest difficulty in shaking off the asthma. Although the crises at such times are less marked, they last longer and chronic bronchial inflammation may be established. The asthmatic sufferer becomes a permanent spitter and cougher.

This condition of complicated asthma may lead to emphysema; the lungs become permanently distended; blood circulation around the alveoli is seriously disturbed; the right ventricle, which propels blood through the pulmonary artery to the lungs, works against growing pressure and becomes progressively fatigued. The patient suffers from respiratory and then cardiac insufficiency. Failure of the right ventricle is unfortunately irremediable.

Attack on the bronchioles

What happens during a crisis can be seen by direct examination of the bronchi. Bronchoscopy shows that the internal lining of the large bronchi is swollen and red. Microscopical study of a fragment of mucosa shows oedema[1] and the presence of many cells, among which are oesinophil polymorphonuclear[2] cells. with acidophil granulations. Small vessels are distended and filled with red cells. Mucous glands function strongly, causing expectoration.

These inflammatory changes extend throughout the bronchi to the sublobular[3] bronchioles, the diameter of which is barely a millimetre, causing partial obstruction. Air enters the bronchiole on inspiration because the diameter enlarges, but it can get out again only with great difficulty because the lungs, in breathing out, flatten the bronchioles. The swollen lining squeezes the opening obstructed by secretions. This is why it is difficult for an asthmatic person to breath out.

But this is not all. Another important factor in the obstruction of the bronchial ducts is the contraction of the smooth muscles which surround them like a ring when secretions penetrate into the lobule. Inhalation of acetylcholine[4] increases this spasm; inhalation of adrenalin[5] stops it.

In serious asthma crises the innumerable outlets are swollen, contracted and blocked with thick secretions, so that hardly any air is able to pass. It is not surprising, therefore, that the asthmatic person becomes asphyxiated and may die.

The origin of lesions

The most minute histological study fails to provide any information about the cause of these deteriorations. The explanation must therefore be sought elsewhere. Clinical analysis reveals three convergent facts:

1. Although they are not among the most numerous sufferers, in some persons asthma

(3) Sublobular bronchiole: *part of a bronchiole above a lobule. It penetrates and branches out inside the lobule as far as the alveoli.*

(4) Acetylcholine: *a chemical substance that is the normal excitant of the parasympathetic nervous system along every pathway.*

(5) Adrenalin: *a chemical substance of the catecholaminic group secreted by the central portion (medulla) of the suprarenal glands. It is a specific excitant of the sympathetic system.*

(6) *Immediate hypersensitivity: see the preceding chapter on 'Hypersensitivity'.*

(7) Antigen: *a substance foreign to the organism which, once inside the internal medium, causes the appearance in the body fluids of an antagonist substance of a globulin nature called antibody; this reacts specifically to antigen.*

(8) Polysaccharide: *a large molecule formed solely of carbon, hydrogen and oxygen atoms and excluding nitrogen. Polysaccharides are classified as 'sugars'.*

arises from inhaling dust or pollens at certain times of the year.

2. In two cases of asthma out of every three, there are histories of asthma or signs of cutaneous hypersensitivity (eczema or urticaria) in the sufferers' families. A genetic factor is therefore involved.

3. Signs of irritation of the respiratory mucosa higher up than the bronchi are often noted in the intervals of crisis (coryza or spasmodic tracheitis). The inflammatory process thus extends throughout the respiratory mucosa; it is not solely bronchial. An injudicious operation on a turbinal in the nose may convert a simple spasmodic coryza into asthma.

These facts lead to the supposition that hypersensitivity to substances contained in inhaled air may be the cause of the generalized inflammation of the respiratory mucosa.

Biological research has made it possible to find in asthmatics the required conditions for setting up a hypersensitivity of the immediate type,[6] including the kind formerly called (by Coca) 'atopic'.

Inhaled antigens

Inhaled antigens[7] are to be found in the external environment, and the air that is breathed in causes them to penetrate the bronchi. The largest particles (10 to 30 microns) are deposited on the lining of the bronchus. They are wafted towards the glottis by the automatic 'sweeper' mechanism consisting of vibratile cilia, beating in a double-layered film of mucous. The vibration of the cilia lasts 8 to 12 seconds, so that particles are carried at the rate of 5 to 7 waves per minute. These waves take one minute to travel a distance of 0·25 to 1 cm in the bronchi. Only the finest particles (1 to 3 microns) reach the terminal bronchioles and the alveoli.

The table on page 50 shows the great variety of 'allergens', ranging from pollens (their role, though interesting, is not essential) to domestic allergens, among which house dust is responsible in eighty per cent of cases. Composed of multiple debris of mineral, vegetable, or animal origin, it contains a specific polysaccharide[8] substance, the chemical composition of which is constant, whatever the initial nature of the dust, and which appears to be the true allergen.

The remaining twenty per cent of cases are due to allergens from litter, animal hairs, and moulds, often found affecting people living in the country.

Most occupational antigens are from vegetable dusts, such as wood-dust particles from saw mills, cereal dusts from silos, flour in bakeries, iris root in cosmetic factories, pyrethrum in insecticide works, tobacco and sugar cane, and the castor oil plant, which is used for many industrial purposes.

The most recent examples of occupational antigens are antibiotics, which are extracted from certain moulds. But for some time other therapeutic antigens have been known, such as ipecacuanha, which is often the cause of allergies in doctors and pharmacists.

In some countries dust arising from large quantities of dead insects is also antigenic. Sometimes it is not crude animal or vegetable products to which people are sensitive, but chemical substances with which they become impregnated, such as naphtha balls (paraphenylene diamine) in the case of furriers, or cigarette-paper in smokers.

Every asthmatic person is sensitive to more than one allergen. During a lifetime, the asthma sufferer will contract successive allergies to different substances. This is not an accidental phenomenon: genetic predisposition facilitates sensitization to exogenous antigens.

Other antigens

Asthmatics are also affected by allergens that are not inhaled. The bronchial apparatus can be attacked from inside, as can any other tissue, because the arteries that irrigate it come from the general circulation and branch off from the aorta.

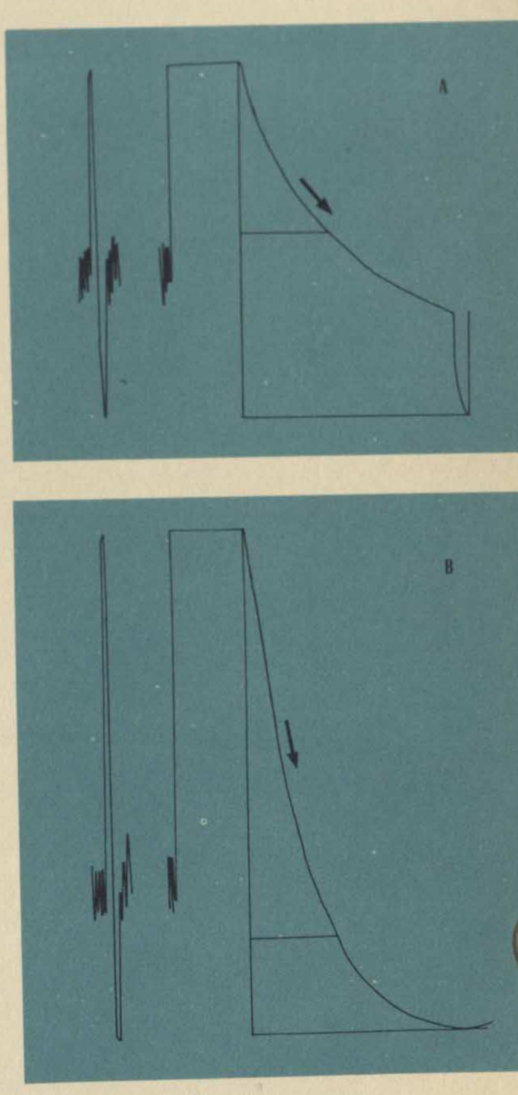
There are also many occasional antigens, such as medical preparations in contact with the skin, or used for injections, hormones being one example. Substances introduced by insect bites are often responsible.

Food products may also be involved. It is commonly observed that a diet rich in milk, butter, cream and eggs can predispose to allergies, even in adults. It is possible that the true allergens may not appear until the food is broken down during digestion.

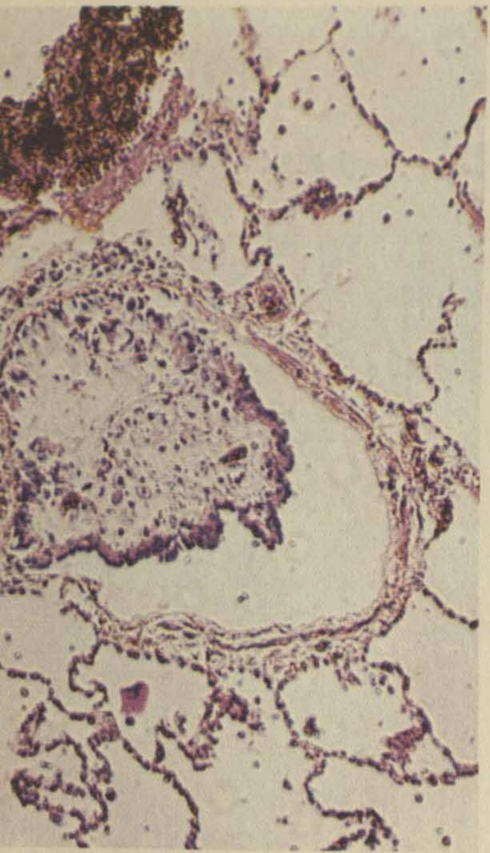
Invasion antigens

Endogenous sensitization may be caused by allergens derived from intestinal parasites, fungi, or invading bacteria. Most important is sensitization to *Candida albicans*.[9] In our climate, this allergy is found in forty per cent of asthmatics, who are at the same time afflicted by chronic bronchitis. Of course, this fungus also affects a large number of people who are not asthmatics.

Substances produced by bacteria such as streptococci,[10] and, less often, staphylococci,[11]



Above, prolonged expiration curve in an asthmatic; below, normal expiration curve. In asthma, the amplitude of the vital capacity is reduced.



Transverse section of a bronchiole in an asthmatic. In the centre, a mucous plug surrounding macrophage white cells. (Photo Lod).

cause sensitization, and as these cocci easily invade the respiratory mucosa and settle there, they can cause bronchial allergies.

The field covered by antigens is immense, so it is easy to understand that identification of a substance responsible for sensitization is often difficult.

Antibodies

Whatever the manner in which antigens are introduced into the body, they penetrate the internal environment and set the protective mechanism in motion, causing the formation of circulating antibodies known as reagins. As a rule, these neither precipitate nor neutralize the antigen; they are destroyed by heat (within thirty minutes at 56°C); they are able to sensitize the skin selectively by passive transfer of serum from an allergic person to the skin of a normal person.

Antigen-antibody reaction takes place especially in the bronchus where there is excess antigen. This reaction results in the release of irritants, principally histamine, which cause oedema, vascular disturbances, and smooth-muscle spasms. This accounts for the local inflammatory bronchial lesions found in cases of asthma.

In order to discover the antigen responsible, an antigen-antibody reaction is induced, either by injecting antigen into the skin (this causes reaction because hypersensitivity is a generalized phenomenon), or by causing the patient to inhale the antigen so that it comes into direct contact with the bronchial mucosa. This is not an easy method, but it is more precise and much more sensitive. Very small amounts of antigen must be used, so that only slight inflammatory reactions occur.

Thus it can be seen that immediate hypersensitivity is an essential factor in asthma: it is impossible to be asthmatic without being allergic. But asthmatic hypersensitivity is not confined to the immediate type. Delayed hypersensitivity also plays a part. This is especially true of bacterial and mycelial antigens (such as *Candida albicans*).

However strange it may seem, the biological explanation of asthma based on the central factor of hypersensitivity is nonetheless unable to account for the general development of the illness or for the intensity and variety of its symptoms. It has been demonstrated many times that if an asthmatic person is subjected to a process of desensitization, his asthma often improves; but this does not occur regularly. Quite often the asthma reappears. The gravity of the crises is not proportional to the extent of the allergy. In bronchial inflammations of allergic origin, whether complicated by infection or not, the symptoms are sometimes slight, sometimes violent. An essential element of the illness thus eludes analysis.

The psychological factor

However strange and difficult to admit, it is in a psychological disturbance that this essential factor must be sought. The nervous system controls the intensity of the crisis because the 'effector' mechanism of the crisis depends upon it. Acting like a wave modulator, it can turn a local bronchial lesion into a slight disturbance, or it can increase it enormously. Violent and prolonged crises are always linked with previous states of psychological anxiety, depression, or considerable excitement.

For many years, nervous disturbance has been observed in connection with asthma, but the classical tendency in medicine of taking into account only the organic and tissue changes to explain symptoms is so deeply rooted that it has been supposed—without it ever having been formally demonstrated—that nervous symptoms were also related to irritant lesions to be found in particular nerve formations, for instance, in the parasympathetic system, or in reticular substance. But no clear correlation has ever been established between this hypothetical disorder and symptoms.

But a connection is to be found if the psychological factor is taken into account. The part that it plays has been so badly misunderstood by psychiatrists, psycho-analysts and others that medical practitioners who regard themselves as strictly objective are still sceptical of such a connection.

It is our view, simple and based on results, that in order for asthma to appear, a person must certainly be allergic; but in addition, and even more important, before the emergence of an asthmatic crisis, an intimate and affective emotional conflict lasting a certain time has to occur in that person. The patient cannot accept the fact that he is affected, but he either cannot or will not take the necessary decisions required to abolish the conflict.

In this state of prolonged indecision the innate anxiety of the asthmatic person becomes considerably increased. If he does not face his conflict, he will repress ('interiorize') the anxiety. As soon as the first crisis occurs, physical anxiety is added to emotional anxiety. Frequently both patient and doctor take only the former into account, whereas the decisive factor in the development of asthma is the one

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(9) Candida albicans: *a mould that frequently infects mucosa, especially in the digestive tract; in children and invalids it causes the disease known as thrush, characterized by the formation of white plaques.*

(10) Streptococci: *bacteria in long chains, involved in many infectious diseases (angina, scarlet fever, acute rheumatism and nephritis).*

(11) Staphylococci: *bacteria that cause furuncle, boils and many purulent infections.*

(12) Neurosis: *a permanent nervous disturbance of personality.*

(13) *See the article on this subject, by Bernard N. Halpern, page 66, Volume 7.*

which the patient does not reveal. The conflict therefore continues and the crises are repeated.

If the crisis is not resolved it will lead to deep psychological depression and the asthma will become permanent. The nervous system becomes exhausted and death may result from sudden 'inhibition' of the respiratory centre. The insufficient supply of oxygen caused by the spasmodic blocking of the respiratory mechanism puts the nerve centres at the mercy of this failure.

If, on the other hand, the conflict is resolved either by circumstances that diminish the traumatic factor, or by reinforcement of the patient's will by psychotherapy, the asthma will cease progressively and often suddenly.

The asthmatic person has greater difficulty in resolving this personality problem than other people because while he receives from his ancestors the genes responsible for allergic hypersensitivity, he also inherits a particular emotional disposition.

The patient should therefore have explained to him the direct relationship that exists between his unadmitted problem and his condition. He must be helped to resolve the dilemma. It is useless to subject a patient to psycho-analysis which would fill him with anxiety, for in spite of what has been claimed, asthma is not a neurosis.[12] The patient knows the terms of the conflict, but is not aware of the direct connection between it and the crisis, which is psychological as well as respiratory. In addition, he very often lacks the strength to overcome the conflict underlying his anxiety. He must therefore be given active psychological support to help his weakened personality to overcome his conflict. Pharmacodynamic medical preparations are then able to play their part.

Treatment

It must not be expected that asthma will be eliminated by drugs. Certain preparations will, however, alleviate the symptoms. The least harmful tranquillizing preparations should be used, especially those that are unlikely to start sensitization. Sometimes, because of a desire to obtain tranquillity at all costs, death has occurred. For example, in a serious crisis, morphine would paralyze the respiratory centres and might be responsible for fatal syncopes. It is better to use barbiturates, which calm anxiety.

Treatment with suprarenal or pituitary hormone (A.C.T.H.) acts only on the symptoms and is not curative. It diminishes the bronchial inflammation resulting from allergy, but if it is indefinitely prolonged it causes metabolic disturbances (water and electrolyte retention and bone disorder); it also causes very marked endocrine disturbances which affect the pituitary and thyroid glands and the suprarenal cortex. The secretion of the latter is stopped and can only be started again with great difficulty. Also, when the organism is saturated with such cortical hormones, the principal risk is that concurrent infection, which is always possible, may become serious and incurable.

Well-controlled desensitizing treatment in accordance with modern methods is the best course to adopt.[13] But of course its efficacy is only partial because it acts on only one factor.

If asthma is to be reduced, the psychological factor, which is the essential factor governing the intensity and recurrence of the crises, must be dealt with at the same time. There is no doubt that a great deal of progress has yet to be made in this field. Very remarkable results have been and will be achieved, as long as medical practitioners understand that the disease is caused not only by phenomena affecting organs and tissues and also know how to deal with the nervous system and hypersensitivity.

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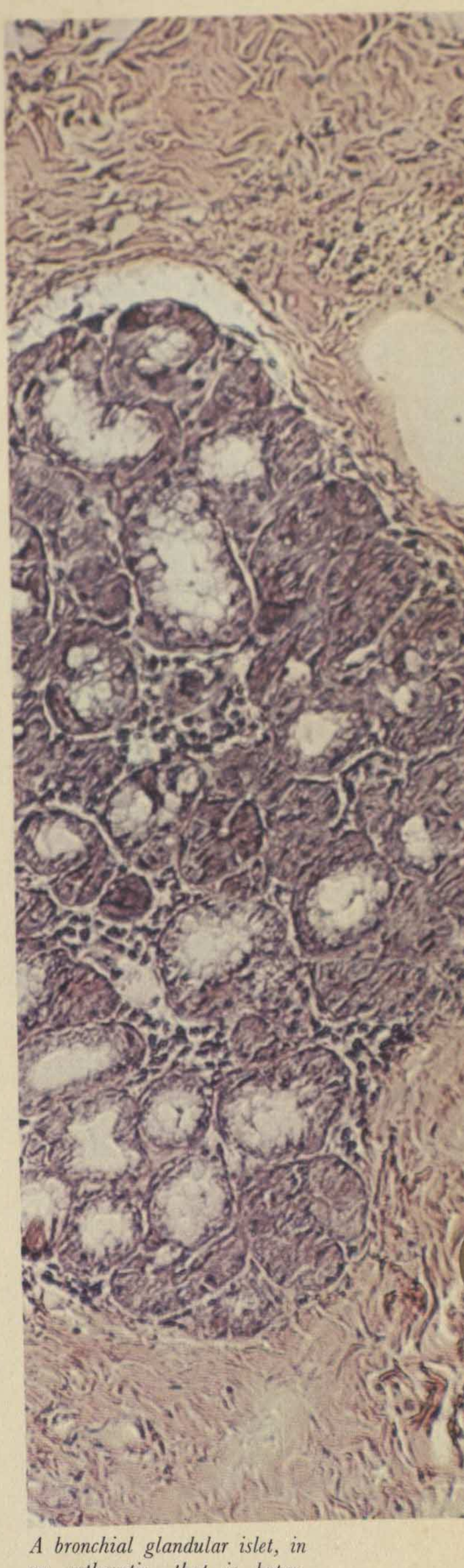


A bronchial glandular islet, in an asthmatic, that is hypersecreting. Clear areas show the hypersecretion of gland cells. (Photo Lod).

Man and dusts

André COLLET

Diseases caused by dust inhalation, and particularly by mineral particles, provide a striking example of the ever-present opposition of the external world to the living organism. Biological reactions to penetration of the lung by such particles and to their chemical composition lead to progressive inflammation and sclerosis. Preventive measures are not always successful, but thanks to precise physiological indications it is now possible to detect such diseases in good time and save sufferers from the action of these harmful substances.

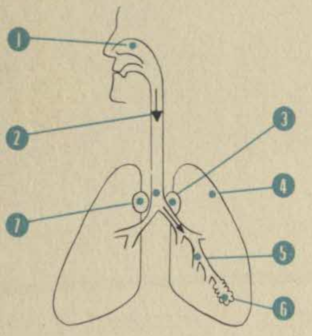


Fig. 1. Diagram showing where dusts settle in the broncho-pulmonary system. 1. Retention and filtering by the nasal fossae; 2. Filtration and broncho-tracheal reactions; 3. Lymph-node reactions; 4. Pleural reactions; 5. Bronchiolar reactions; 6. Alveolar reactions; 7. Transfer to lymphoid and other organs.

Although the human organism is apparently an independent entity, it is, in fact, linked to the external environment, depending on it closely for nutrition and the oxygen that it inhales. The wonderful architecture of the human body channels a flow of water, as well as mineral, organic and gaseous matter, in contact with sensitive and fragile permeable structures. These consist of a layer of cells, 30 microns thick in the intestine, and an even more tenuous barrier—one tenth of a micron—in the alveolar wall of the lungs.

Despite their offering a great deal of protection, these essential permeable membranes are points of weakness, allowing the entry not only of nutritional and respiratory requirements, but also undesirable substances or particles. As Policard said, it is a real conflict between external world and living organism.

Dusts

In normal life, man does not usually have to breathe very dusty atmospheres, although the problem of air pollution in big cities is considerable. But at work man is often subjected to a genuine risk, inhaling mineral or organic particles. This leads to special problems of pneumoconiosis, or pulmonary diseases caused by dust. As well as the human problems posed by these diseases, there are economic and medico-legal aspects to be considered.

The natural sources of dust are of little importance. It is the artificial or industrial sources that must be considered. Smoke or harmful dusts are produced by the mechanical destruction of hard materials. The greater the energy used in grinding and the harder the material, the finer and therefore the more dangerous are the resultant particles. Mechanization, in other words, has contributed to the multiplication of dust diseases.

The size of the particle is the most important physical factor relating to dust diseases. In pneumoconiosis, size varies from a few hundred angström units to approximately 10 microns. The behaviour of dusts is governed by their dimensions when, as aerosols, they are suspended in air or in liquid. Size is also a determining factor in dust-lung relationships.

The second important factor is that of the surface of the particles and their physico-chemical properties. What kinds of dust are habitually found in cases of lung disease caused by mineral substances? There are soluble dusts that are rapidly absorbed into organic liquids; non-toxic, like those in potash mines (KCl); these do not present any problem. On the other hand, certain arsenicals or manganese compounds can cause general poisoning.

Insoluble dusts stay in the organism for an indefinite time. When inert, like coal and certain silicas, they act by blocking the organism. When harmful, like free silica (SiO_2), they cause degenerative and fibrous lesions of the lung. If the bodies inhaled are radioactive, they present the very serious problem of the starting of lung cancers, and of general blood disturbances through beta or gamma radiation.

The problem of vapours and smoke is more indefinite. Here, acute toxic disturbances are involved which are not localized in the lung.

Lung and dusts

If the particle concentration in air breathed in and air breathed out is measured in a man working in a dusty atmosphere, a difference is observed—the air that is breathed out contains less dust. There is retention of particles in the respiratory system. A more detailed examination shows also that every type of dust is retained to an equal extent.

Heubner observed in 1920 that lung retention of particles, on which the whole question of diseases from inhalation rests, depends above all on the size of the particles. Size is the essential factor in the accumulation of dust in the lungs.

Research carried out, largely on human beings, between 1948 and 1952 in the United States by Van Wijk and Patterson, Hatch and Hemeon, Wilson and La Mer, has shown that retention is brought about by two kinds of structures, each possessing a different function; the air passages and the lung alveoli.

Practically every particle of a size greater than 5 microns is retained by the upper air passages; that is, they become trapped in the nasal mucosa or in the mucosa of the large bronchi (coefficient of retention 100 per cent). But as the depth of penetration of particles is in inverse ratio to their size, the finer they are, the further they go. In the alveoli, there is a maximum probability of fixation of particles in the vicinity of one micron (60 per cent). Above this size, retention is reduced; below this size it is also diminished (25 per cent for 0·5 micron). Agreement has not yet been reached on the fate of the finest particles, called infra-micronic. Perhaps they are strongly retained, but at these sizes, agglutination phenomena become very important.

Let us now penetrate with the particles into a lung alveolus enlarged to our own size. It looks like a vast room with slightly mobile walls, damp, with a dense network of lung capillaries in relief. Large, immobile cells with finger-shaped processes protrude from the walls. These cells are set in the general covering of the walls. Other cells are free and move slowly on the surface. The air of this chamber is renewed by diffusion, not by any ebbing and flowing of air. Solid particles have penetrated here with the slow renewal of the alveolar air by fresh air, impelled by Brownian movement; the finer the particles, the greater the movements. Some of the dust goes out with the stale air, some of it sticks to the surface of the walls. Particles of the latter type are then collected one by one by the mobile cells, which ingest them by phagocytosis and accumulate them as they move along. Other particles of dust penetrate directly into the thickness of the alveolar wall.

The first contact between mineral particles and living organisms is made through phagocytosis: this cleans the walls but unfortunately concentrates the dust, a fact that bears heavy consequences.

What happens to these cells (macrophages) charged with particles? Some remain in the alveolus and make their way through the lung in this way by causes little understood. Others insinuate themselves into the tissue spaces where lymph flows, and accumulate in certain preferred places such as the peribronchiolar linings, where they form large deposits. Some macrophages reach a cul-de-sac in the pleura or, outside the lung, they reach the lymph nodes of the thorax. Other dust-containing cells may happen to reach the opening of the terminal bronchioles. They then ascend the air pathways and are expelled. This is the important mechanism of lung cleansing.

Lung cleansing is carried out by two different mechanisms. The first is via the air pathways (trachea, bronchi and bronchioles), which contain very efficient means for transporting particles and cells containing dust: the vibratory cilia. The second mechanism, in the alveoli, is poorly equipped and it would seem that cells and particles are eliminated from them only by chance, for it has no special organs. This very slow and inefficient form of

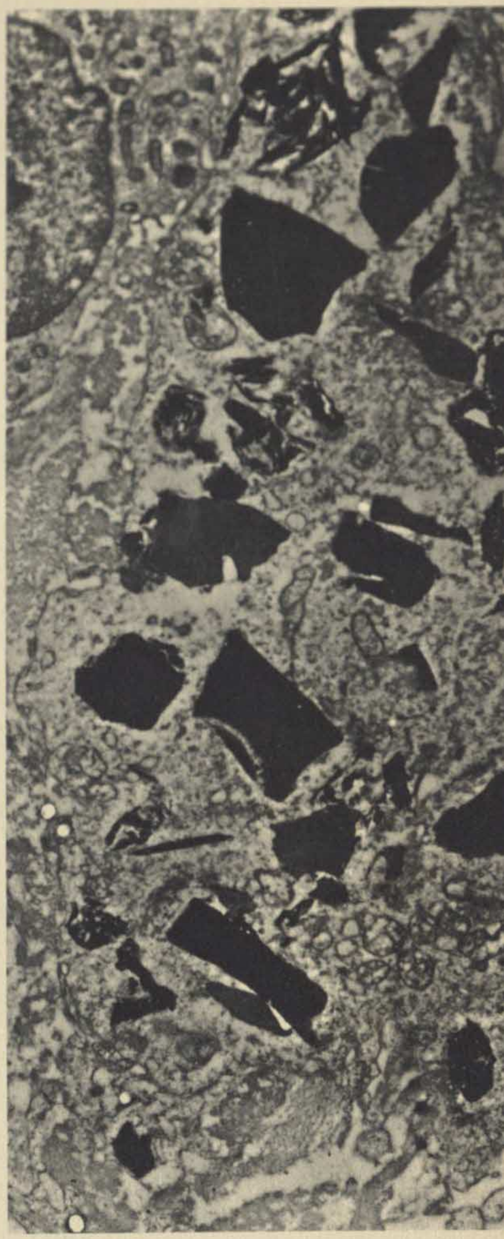
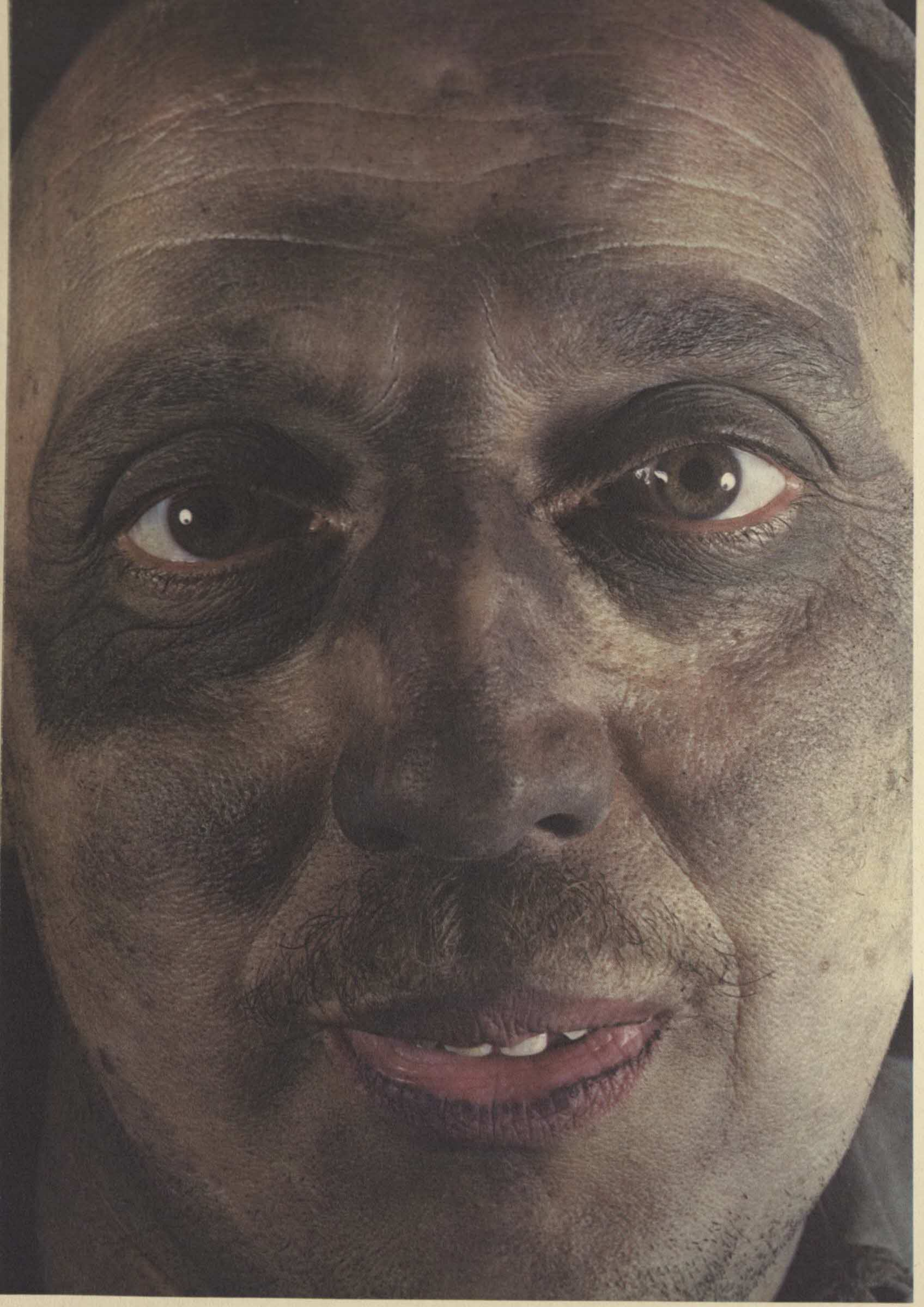
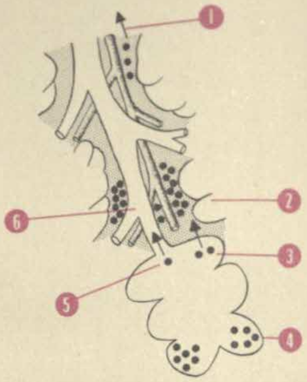


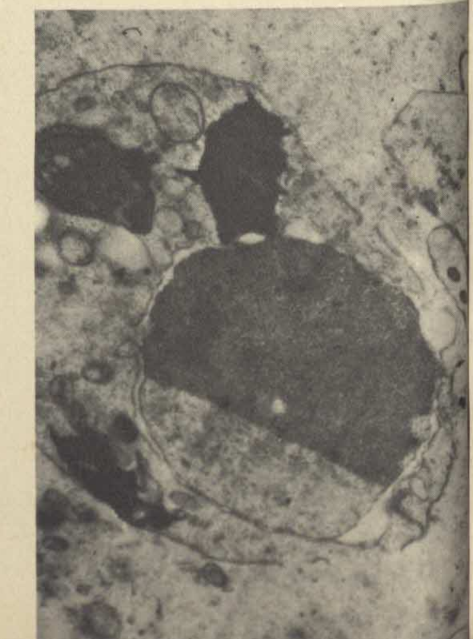
Fig. 2. Electron micrograph of a cell exposed to dust in the lungs of a coal miner, showing phagocytosed particles (coal and other minerals), as well as intact cytoplasm of the cell.





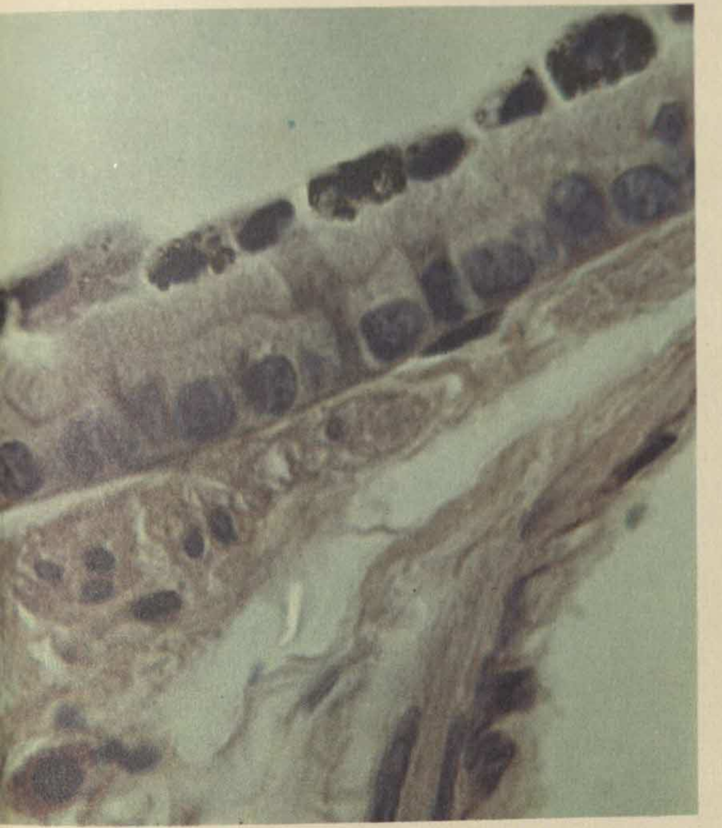
This diagram shows the fate of particles inhaled at the level of the pulmonary alveolus; it also shows respiratory function disorders, in particular emphysema, or permanent dilatation of alveoli and bronchioles. 1. Direction leading to the lymph nodes or the pleura; 2. Perifocal emphysema; 3. Transit through the peribronchiolar connective sheath; 4. Accumulation in the alveoli; 5. Return to the bronchial branches (filtering); 6. Lobular emphysema.

Electron micrograph of a dead cell following ingestion of silica; note destruction of normal structures (nucleus and cytoplasmic bodies).



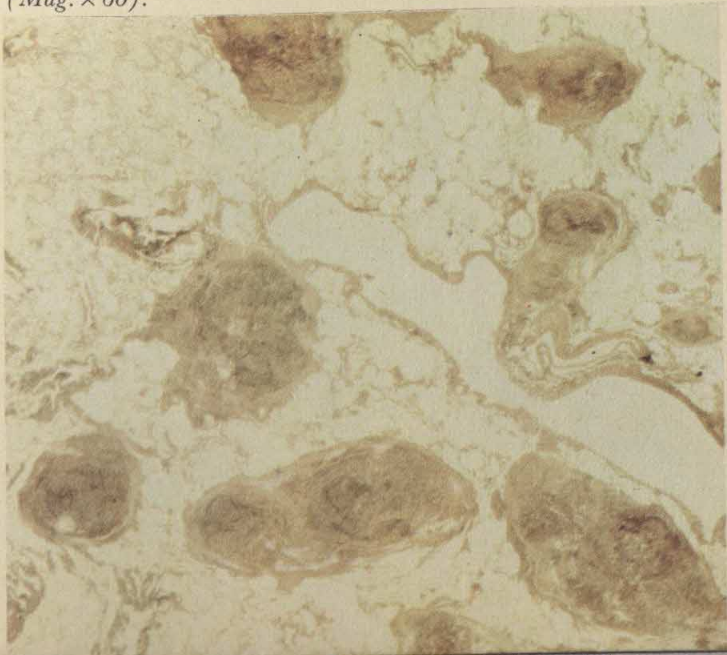
Silicosis

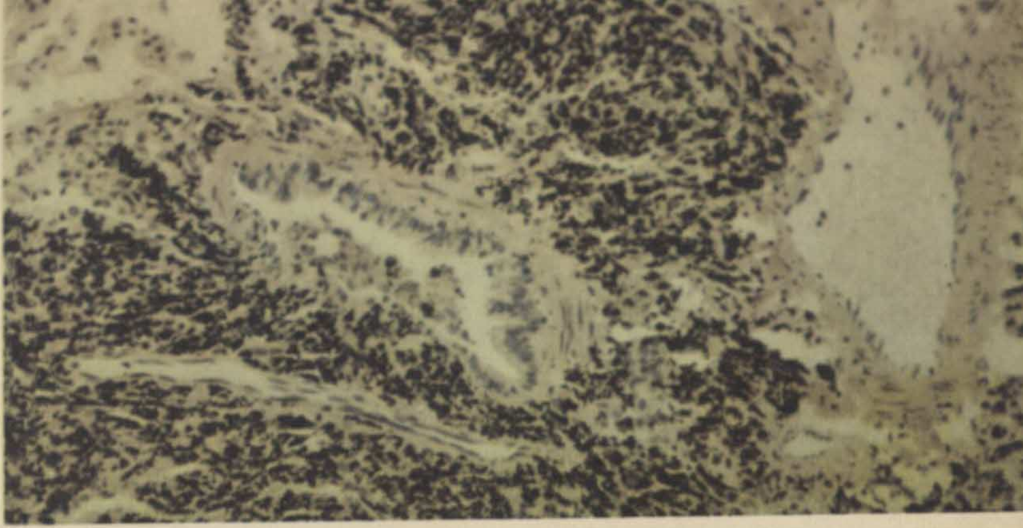
These photographs were taken at the laboratory of the French Coal Study and Research Centre. (Photo Lod).



Elimination of cells containing dust (black marks) by the moving carpet of bronchiolar vibratory cilia (rat exposed to titanium dioxide dust). Stain: alum-haematoxylin-eosin orange. (Mag. × 1,500).

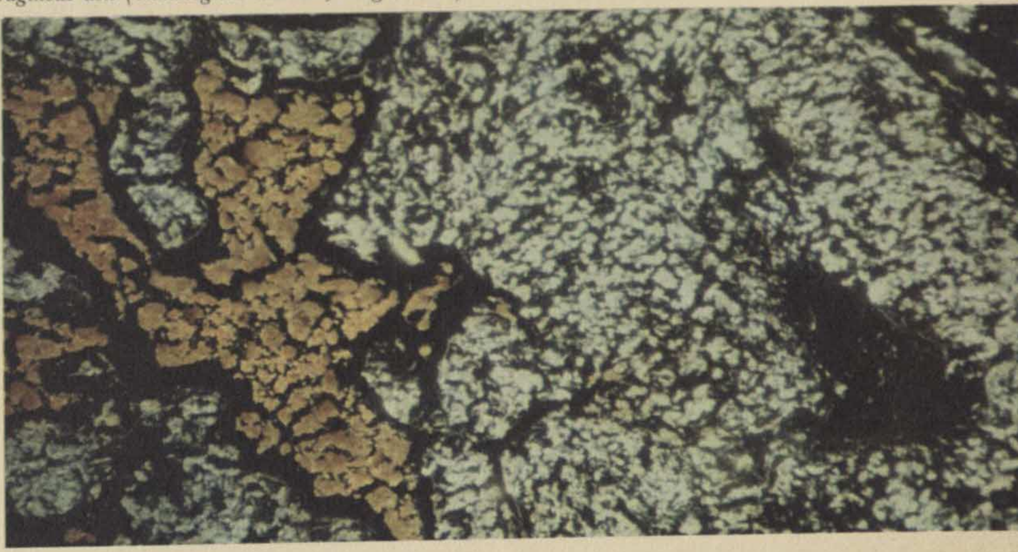
Human silicosed nodules: clustered pellets of collagen fibres, separated by aerated lung. Stain: Van Gieson. (Mag. × 60).



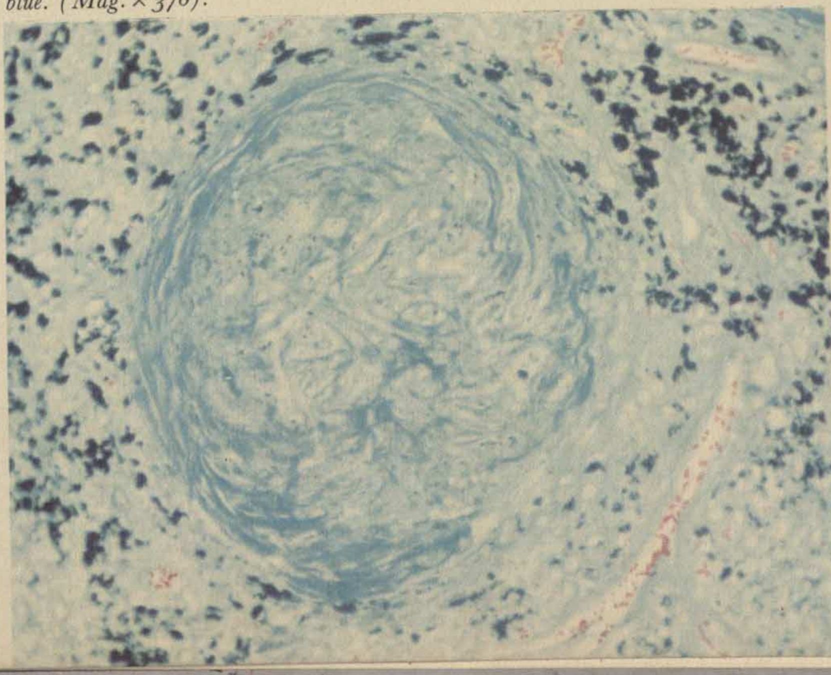


Pneumoconiosis nodule in a coal miner. The small black marks represent silhouettes of cells containing dust massed around a damaged bronchiole and an artery. Stain: alum haematoxylin-eosin orange. (Mag. × 200).

Mineral content of the nodule in the previous illustration, after micro-incineration of the histological section. Note the large amount of white ash and the presence of red ferruginous ash (radiological contrast; mag. × 200).



Detail of human silicosed nodule: note whorled arrangement of fibres, here coloured blue. The nodule is surrounded by cells containing coal dust. Stain: Mallory's acid methylene blue. (Mag. × 370).



cleansing is a serious handicap to the function of total lung purification. Nevertheless, this function has a capacity that must not be overlooked. As far as can be calculated, a miner, by the end of his career, ought to have retained two hundred grams of dust. But not more than approximately fifty grams, on an average, will be found in his lungs.

Silicosis

What happens after retention depends on the type of dust involved. If it is inert, deposits form which congest delicate organs like the bronchioles, or expand them, leading to a condition known as emphysema. If the dust is harmful, as in the case of certain types of free silica (SiO_2), it destroys the cells that have concentrated the dust particles by phagocytosis, or those grouped round the dust, and sets up the destructive and fibrous reaction typical of silicosis.

Silicosis lesions consist of nodules of thick spiralling fibres without cells. Lesions caused mainly by inert dust are made up of a mass of phagocytes situated round the bronchioles or pulmonary vessels.

At this stage, pneumoconiosis has little effect on either the circulatory or ventilatory functions of the lung. Any disturbance is compensated for by the natural excess of lung parenchyma. Unfortunately, however, things do not remain in this condition and complications of varying frequency and rapidity ensue.

In cases of true silicosis, or of varied pneumoconioses, the major complication arises from the concentration of tiny nodules into one or several masses which can become as large as a man's fist.

Because of their appearance under X-rays these masses, which resemble pulmonary cancers, are called pseudo-tumours. Their effect on respiratory and circulatory functions is dramatic; within a short time the patient is unable to function normally and then death ensues.

The origin of these pseudo-tumoural condensations has given rise to much controversy and has still not been definitely established. It seems fairly certain, however, that tuberculosis plays a large part in their formation—tuberculosis that is often detectable, but in many other cases impossible to prove. However that may be, tuberculosis and other lung infections do arise in this serious development of the disease. The term used in English is 'infective pneumoconiosis'.

A new idea, which has been gaining ground rapidly, suggests that a dust-impregnated lung is easily susceptible to various infections. Under these conditions infection is aggravated and treatment is of little use (Gernez-Rieux).

Because silica is the most harmful dust and apparently the one with the most unusual toxic effects, it has been and still is the subject of most research, but we are still far from reaching a definite conclusion about it.[1]

The manner in which a particle of silica exerts its toxic action (soluble products and physical surface action) does not exclude other secondary mechanisms. There is, in addition to the direct action of the particle, an extraordinarily long and complex chain of physico-chemical reactions in cells and tissues. But we are still ignorant of many of the links in this chain.

On the other hand, owing to the progress of research, silica is now no longer regarded as being very different from other disease-causing factors. It takes its place among other mechanisms of general pathology as a common inflammatory agent, producing fibrous agglomerations. A silica particle may be likened to a mineral bacterium.

Diagnostic problems

As long as the function of the lung is not gravely impaired, the symptoms of pneumoconiosis are reduced to a slight cough and bronchitis. Later on, breathlessness (dyspnoea) predominates and prevents any exertion.

The importance is too often forgotten, sometimes even by the patient himself, of pinpointing the occupation or occupations which have given rise to the risk of pneumoconiosis, as well as the length of time spent working under this risk. This occupational anamnesis is nevertheless one of the keys to diagnosis.

The essential test for someone suffering from pneumoconiosis is still radiological examination. In practice, diagnosis depends on the X-ray plate and a great deal of research has been carried out on this subject, as much from the point of view of classification of lesions (seriousness and prognosis), as from that of diagnosis of other disturbances that present similar pictures on the X-ray screen.

Radiological diagnosis between silicosis and other pneumoconioses is extremely desirable, but is still not possible to achieve with certainty. The correlation between radiographs and anatomo-pathological data is at present being studied and this should produce very useful clarifications.

It must be remembered that radiographs

(1) *Not all forms of free silica are equally dangerous biologically. In general, the natural hydrates (fossil silica and opal) are practically harmless, but the anhydrous forms, whether they are crystallized or not, are markedly toxic.*

Experimental work shows that silica is capable of killing phagocytes. The first explanation of the harmful effect of silica was that the edges of the particles wounded the ingesting cell. This hypothesis was made untenable by the observation that silicium carbide particles, which are very sharp, did no harm. A chemical explanation was then suggested. The very weak solubility of silica might free a substance that was toxic to the cell, spread from the particles and kill neighbouring cells and phagocytes. This was the theory of solubility (Gye and Purdy, Gye and Kettle, 1922). But here also discrepancies appeared that gave rise to another theory, purely physical, suggesting that the surfaces of the particles were active in consequence of properties other than those of hydration (Jaeger, 1950).

It is now thought that a possible explanation is to be found in a theory of reduced solubility at the surface of the particles; that is, that on the surface there might be toxic quartz granules of the silica hydrate which destroyed the cytoplasm of neighbouring cells. Actually, only phagocytosed particles appear to be toxic.

are produced by absorption of X-rays, sometimes selectively and by contrast with nearby structures. Anatomical lesions cannot therefore be directly superimposed on X-ray pictures. For example, coal is transparent, as is a fibrous tumour; but iron (in the blood) and calcium are opaque.

X-ray examination remains a basic technique in the development of methods for diagnosing pneumoconiosis, but it was quickly recognized that radiological indications and disturbances of lung function are not always parallel. The problem of disturbance of lung function has therefore to be regarded as a whole, and again, this has been the origin of long and laborious research.

Ventilation difficulties were first considered, then the renewal of alveolar air. At present, the problem is being more closely investigated, though still only in the laboratory, through studies on the capacity of gas to diffuse through the alveolar membrane; that is, through the blood-air barrier.

Disturbances of lung function in patients suffering from pneumoconiosis stem principally from the extension of abnormal fibrosis and from emphysema; that is, from an increase in volume of channels and spaces normally ventilated. From this, there results disturbance of alveolar ventilation, and of replacement of stale air in the alveoli by fresh air. The consequence is a reduction of oxygen and an increase of carbon dioxide in arterial blood. Eventually a diminution occurs in the pulmonary circulation, which becomes especially apparent when any attempt at exertion is made.

A certain number of tests have been tabulated for functional exploration of the lung, for pre-operative surgical or medico-legal purposes, and these allow an assessment to be made of a patient's respiratory capacity at any given moment.

It now remains to consider the development of pneumoconioses. This varies according to the intensity of dust infiltration and the type of dust involved. Very acute silicoses have been observed after three to six months of massive exposure to quartz, causing death after one or two years (Uehlinger, Nicod, 1949-1950). More often, a worker in a sand-pit or a pottery contracts silicosis after exposure lasting from three to five years, the disease developing over a period of ten years.

In coal miners exposed to mixed dusts (coal and silica), some fifteen years' exposure is necessary before pneumoconiosis appears, which then develops over a further period of fifteen years. These figures are only indicative, as complications may shorten the development, or favourable conditions may prolong it. Infection in the development of pneumoconioses is certainly one of the fundamental factors to remember in the treatment of lung diseases caused by inhalation of dust.

Prevention and treatment

Prevention can be considered from the point of view of technical measures aimed at reducing dust, as well as of medical measures. Measures aimed at diminishing the production of dust are numerous. The principle on which they are based is that of moistening the materials to be worked (in the processes of drilling, pulverizing and mixing), which in practice has proved by far the most effective. Another method used is dust-suction, relatively easy at permanent work-sites involving chiselling, polishing, and powder handling. Sometimes particles can be precipitated by a powerful static electric field, as in the case of fumes coming from furnaces. For the most exposed occupations, eg, sand-shifters, the wearing of masks or protective hoods is necessary.

The major defect of all these measures is that they are unable to eliminate very fine particles of about one micron in diameter, which fail to be trapped by many dust-prevention techniques, and as we know, they have a high retention coefficient and are very harmful.

Medical prevention is still limited in practice. Systematic examination ensures early detection, elimination of tubercular contaminants and contacts, and redeployment of patients with developing lesions, so that they can work where they will not come into contact with dust.

From the theoretical point of view—and herein lies the future of present-day research—medical research can aim at neutralizing poisonous particles, at reducing tissue-reactions to particles, and at stimulating the cleansing function of the organism.

Treatment of pneumoconiosis is still limited, but two measures are of practical importance; one is the use of various anti-tubercular preparations to avoid tubercular contamination among those in contact with the sick person, and to reduce lesions; the other is surgical treatment of silico-tubercular pseudo-tumours. On the average, when the indications are accurately assessed, about half the patients suffering from pneumoconiosis are nowadays cured.

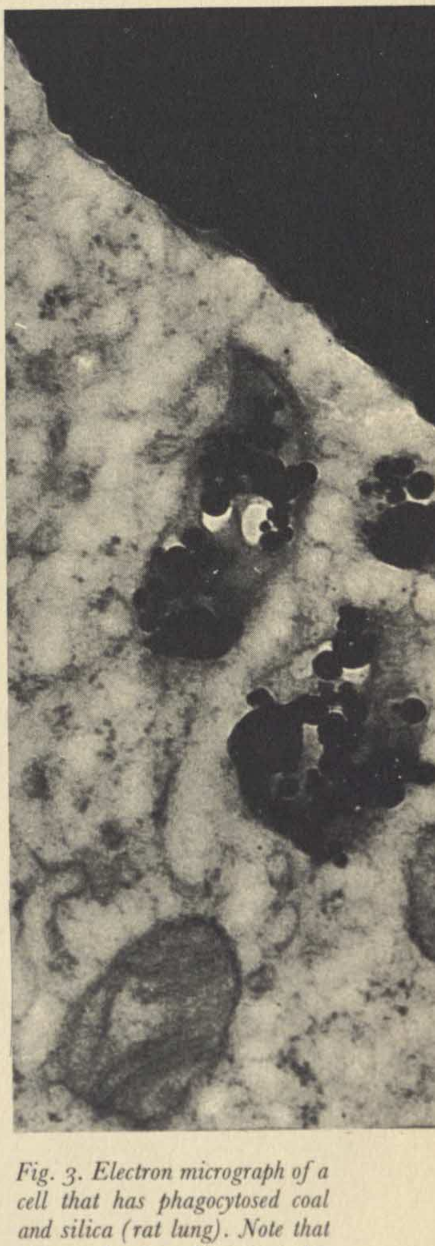


Fig. 3. Electron micrograph of a cell that has phagocytosed coal and silica (rat lung). Note that the cytoplasm touching the coal is intact, while it is thickened round the fine silica particles.

Diseases caused by spores

G. SECRÉTAIN, E. DROUHET and F. MARIAT

Mycoses are infectious diseases, the pathogenic agents of which are microscopic fungi. Compared with bacterial infections, mycoses are rare in man; this suggests that the fungi have some difficulty in adapting themselves to higher organisms. In describing some of their properties, we shall show the principal characteristics of human mycoses.

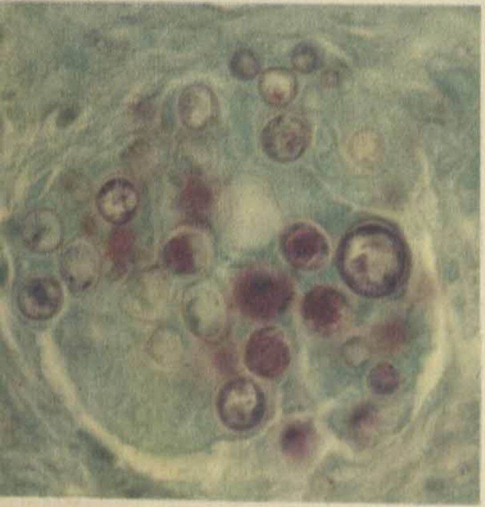


Fig. 1. Black grains of fungal mycetoma in a histological section of a foot biopsy. These are composed of intertwined vesicles and filaments. Haematoxylin-eosin stain. (Mag. × 40).

With the exception of tinea infections, mycoses are not contagious. In nature, the majority of pathogenic fungi live as saprophytes.[1] Some of these are natural saprophytes of man, such as *Candida albicans*, agent of the disease called thrush.[2] This fungus is found naturally in the mucosa of man and becomes pathogenic only when an organism is insufficiently defended. Most pathogenic fungi live in the soil in decomposed organic matter, such as animal excrement, vegetable refuse, etc. Man becomes infected when spores or filaments of fungi penetrate natural apertures, or as a result of a lesion.

Histoplasmosis occurs in the Mississippi and Ohio Valleys, where it has long been known as a rare and fatal mycosis. During the Second World War, lung radiography, which it was obligatory for all conscripts to undergo, showed that a large number of recruits from these regions of the United States were carriers of lung calcifications. As was natural, these calcified lesions were first thought to originate from tuberculosis, but in a large number of cases the tuberculin skin-test was negative. It was then thought that similar tests could be made with a filtrate of a culture of *Histoplasma capsulatum*, the fungus responsible for histoplasmosis, and this result was positive. In certain localities, where more than 80 per cent of the population showed a positive response to the test, the fungus was isolated from the soil and from dry pigeon- and chicken-droppings. In South Africa some speleologists contracted histoplasmosis after having visited caves infested by bats, and the fungus was isolated from piles of their droppings. Following this discovery, a journalist wrote that histoplasmosis was the Pharaohs' vengeance on Egyptologists who had died after penetrating into the tombs of the Pharaohs for the first time; if, for the vengeance of the Pharaohs, we substitute the vengeance of the bats, this hypothesis is scientifically correct.

Blastomycosis is another example. This disease, caused mainly by two substances that form on wooden posts, occurs in Madagascar; one of the fungi responsible, *Cladosporium carrionii*, is found in the dry southern region of the island, which has a rainfall of only two inches a year; the other, *Phialophora pedrosoi*, is found all along the east coast, where it is very damp and the rainfall exceeds eighty inches a year. If it is known where the patient contracted the infection, it is possible to ascertain the kind of fungus responsible.

Fungus morphology

The temperature of the human body obstructs the development of pathogenic fungi. These are ill-adapted to develop at a temperature of 37°C, which is far from an optimum growing temperature for most of them.

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(1) Saprophyte: *a plant organism living on organic decomposing substance.*

(2) Thrush: *a disease of man, characterized by the appearance of whitish spots in the mouth, formed by an intertwining of filaments and yeasts of* Candida albicans *fungus.*

(3) Encapsulated: *surrounded by a capsule, which in microbiology, is a mucilaginous envelope of a bacterium or fungus, outside the membrane.*

The best example is that of encapsulated yeast[3] *Cryptococcus neoformans*, which is killed at 40°C and therefore cannot infect the rabbit, whose internal temperature is too high. On the other hand, the tinea fungi, which do not develop at 37°C, only become parasites of the horny layer of the skin and hair. In short, one can say, though without being certain of the connection between the two facts, that in tropical countries where fungi are more adapted to high temperatures, deep mycoses are found more often than in temperate countries.

In cultivation, at a temperature of 20°C, pathogenic fungi, with the exception of yeasts, occur as filaments with a diameter of 2 to 4 microns and sometimes considerably more. The fungi that preserve this form *in vivo* cause localized lesions in the organism. The agents of generalized deep mycosis have a totally different parasitic phase, and occur in a yeast form that is much more favourable for the invasion of the organism via the blood or lymphatic system. Despite this, mycoses are more often chronic diseases that develop slowly.

The transformation of filaments into yeasts is very interesting and mycologists have reproduced this parasitic yeast form in culture and have studied the conditions of its reproduction, which are different for each parasite. Pasteur was the first to observe the transformation of filaments into yeasts in a saprophytic fungus, *Mucor rouxii*, in conditions of partial anaerobiosis.

Certain mycoses are characterized by the location of the parasite in granules of different colours and sizes, from 300 microns to some centimetres. These are called mycetomas. The disease caused by this parasite is frequent in Africa, where most often it resembles Madura foot. It is characterized by the formation of an inflammatory pseudo-tumour with many fistulas. The pathogenic agents that cause this disease are varied; as well as fungi of very different species, there are also filamentous bacteria, called actinomyces. These different agents penetrate the organism after a lesion, develop gradually in the skin and muscles, and eventually reach the bony tissue which they attack and transform, having found there a particularly favourable environment. Incidentally, it is fairly common for pathogenic fungi to attack bony tissue.

The absence of toxin-production in fungi is somewhat peculiar; it may be due to the thick, often cellulose membrane which surrounds the fungus and prevents any intimate contact between parasite and host, as well as any diffusion of toxins. The parasite cannot therefore cause lesions disseminated at a distance and any that do occur will indicate the presence of the pathogen itself. A subcutaneous or deep mycosis cannot therefore attack a healthy skin.

The presence of a membrane may also explain the feeble production of antigens by fungi in the parasitized organism. The reactions between antigens and antibodies are on a very small scale and give rise to group reactions.

Antifungal antibiotics

Fungi are completely insensitive to antibacterial antibiotics in current use. This insensitivity is a property that enables a laboratory fungus-culture to be freed from bacterial contamination. In man, the use of broad-spectrum[4] antibiotics, by upsetting the yeast-bacteria equilibrium of the intestinal flora, permits the development of *Candida fungi* and thus favours the appearance of thrush, which may spread to the whole digestive tract and even become generalized.

However, it has been discovered in the last few years that there are antibiotics which prevent the growth of numerous fungi without acting on bacteria. Nystatin, one of the first discovered by Hazen and Brown, in 1951, is a broad-spectrum antibiotic used with success in infections of the skin and mucosa caused by yeast of the genus *Candida*. Amphotericin B, injected intravenously, is active in deep mycoses which up to now have proved fatal; it must, however, be used with care and administered under hospital supervision.

The latest to be used in treatment, griseofulvine, has been known for some time. An English research worker, Gentles, was the first to think of using it in the treatment of a guinea-pig affected with tinea. Because the antibiotic, which is very active against dermatophytes, accumulates mainly in the skin and its derivatives, it has been used orally for the last few years in the treatment of human tinea infections. It has revolutionized treatment which would formerly have involved depilation by X-rays or extended local treatment.

Although mycoses in man have been known for a long time, only in the last ten years or so has their importance been revealed. For twenty years they have been the object of much research, not only by doctors, clinicians and epidemiologists, but also mycologists interested in the morphology and physiology of pathogenic fungi.

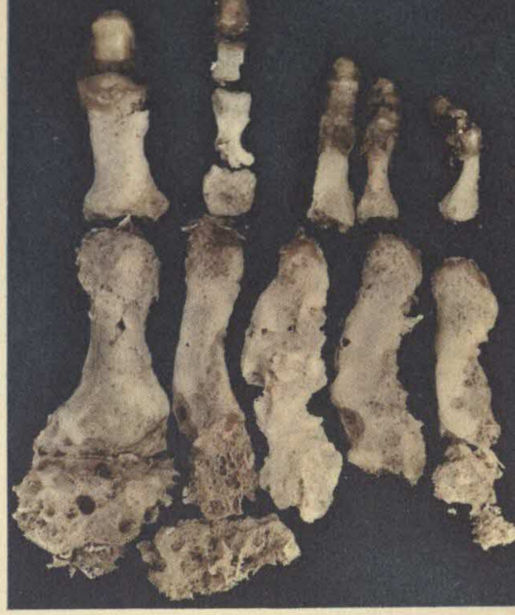


Fig. 2. The bones of a foot attacked by mycetoma fungus. The fungus forms granules in the bones, hollowed by cavities; the bone reacts by producing a substance that causes deformation.

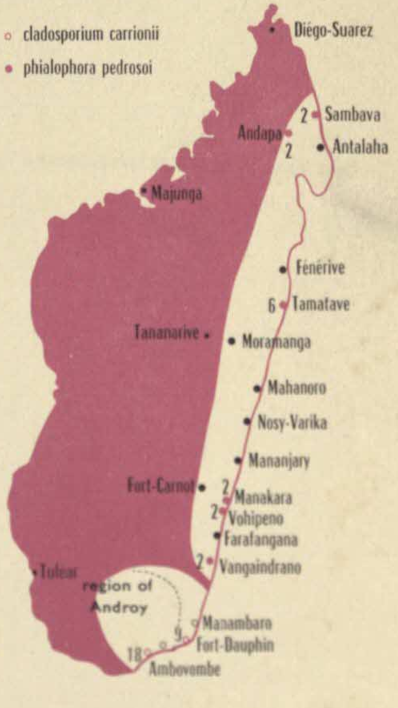


Fig. 3. Distribution in Madagascar of the fungi that cause chromoblastomycosis.

(4) Broad-spectrum antibiotic: *an antibiotic that prevents the growth of a large number of genera and species of micro-organisms.*

Industrial medicine

Etienne FOURNIER

Today, industrial medicine has become so important that all over the world systems of protection, prevention, and insurance have been established, resulting in certain trends in social and collective medicine. Professor Etienne Fournier here shows that this development has become indispensable because of industrial changes, and how, after going through a period of collective consideration, problems are again being considered individually. This chapter must be regarded, however, only as an introduction to a discipline which is still expanding, parallel with the world-wide expansion of industry.

Old medical books discuss wounds, fevers and epidemics in great detail. None of them mentions industrial diseases, except incidentally. In France, in the fifteenth century, with advances in the craft of printing and the manufacture of firearms, there began a development which has not yet ended; this was the progressive increase in the numbers of workers and salaried persons and the decrease in the numbers of the peasantry. Medicine has followed this development.

Doctors from mining regions often studied the problems of industrial medicine; this was done by Ulrich Ellenborg (1473) for the goldsmiths' workshops at Augsburg, by Paracelsus in the Villach district of Carinthia, and by Agricola at Joachimstal and Chemnitz. But their efforts were modest and their lack of chemical knowledge prevented any really serious work from being done.

It was Bernardo Ramazzini to whom we owe the first treatise dedicated and limited to workers' diseases (Modena, 1700), and his claim that, 'So far as I know, no one has surveyed this field' appears to be true. His book sketches the great landmarks of industrial medicine and is a penetrating study of technology and research into the causes of harmful diseases, in which he cites noxious vapours, tiny dust particles, and violent and irregular physical movement. He also makes a study of prevention and treatment which he does not hesitate to base on the conditions of life under the disease called 'poverty'. To this man, so well versed in science and the arts, and a real apostle of our common duty to have pity on and to assist the humblest worker, we owe the fact that the details of a man's occupation have now become part of the doctor's normal approach to diagnosis. It was two hundred years, however, before this sort of diagnosis became the rule. Indeed, until 1850 the industrial inferno of the eighteenth century grew worse with the appalling 'wage slavery' which with all its degrading misery was concentrated in the slums.

The isolated voices of some doctors, such as Charles Turner and McCready in the United States, Chevallier, Patissier, Tanquerel des Planches and Vernois in France, and Dubini in Italy, did little to influence industrial managements. Such improvements as there were, must be ascribed to the humane and intelligent initiative of a handful of industrialists, of whom the most famous was David Dale in his spinning mill (from 1785).

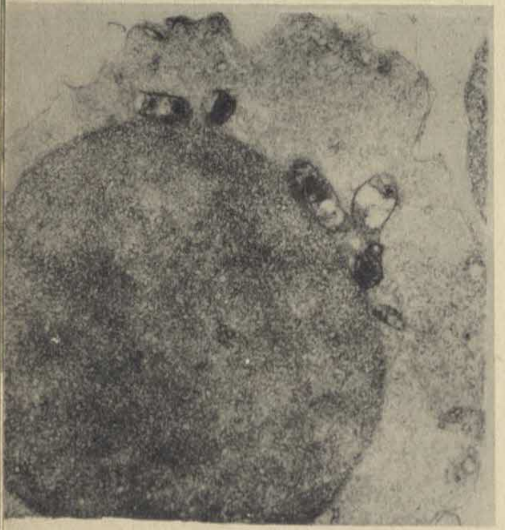


Fig. 1. Lead poisoning is accompanied by blood disorders. Maturation of the poisoned erythroblast is abnormal and iron is not fixed properly during the synthesis of haemoglobin. This is shown in the microphotograph.

Social reforms

During this period, a whole generation grew up with an intense desire for social reform, which then lapsed and was apparently forgotten, only to surge up again more powerfully (and no doubt to remain permanently alert thereafter) in the middle of the nineteenth century. From then on, industrial legislation extended to all countries. At first, this extension was very slow, except in England and in some parts of the United States. Later, it spread more quickly, until at the beginning of the twentieth century there was throughout the civilized world an ample, well-organized and orderly system of legislation applicable to industrial workers.

Industrial medicine became organized a little later, when, in Germany, on the initiative of Bismarck, social laws, introduced in 1883 to combat the more flagrant injustices, began to embody plans for social aid. It was at this time that there came into being a variety of compensation schemes for factory accidents, maternity, sickness, and invalid care, all of which required diagnosis and treatment.

In 1895, it was made compulsory in England to notify the existence of certain illnesses, and compensation for the victims of some of them was made obligatory.

In France, the establishment of various family assistance funds, of social insurance, and then in 1945, of a social security system, gave a widespread and strong impetus to industrial medicine. Since then, it has become an obligatory function, imposed partly on the employer, and dedicated chiefly to the task of diagnosis and prevention.

The relative importance accorded by different countries to the social aspect of industrial medicine explains why it is more highly developed in some countries than in others. In Britain, the first comprehensive system of social security, based on the Beveridge Report of 1942, was introduced in 1948. In countries where industrial development is poor, the introduction of industrial medicine is sporadic and its benefits are devoted more to mining communities and industry than to agricultural workers, to whom its application appears to be difficult and slow.

In heavily industrialized countries, where the percentage of agricultural population has waned, different tendencies become apparent. In North America, traditionally supporting private enterprise and with a great deal of industrial liberalism, a system of extended prevention was established only at a very late stage. Despite its high standard of living, the United States resorted to a system of social insurance only after the great industrial crisis that led to the New Deal.

In Western Europe, where the state as well as managerial associations and trades unions frequently intervene, social security schemes now predominate everywhere, with slight though important differences arising from the need for re-grouping certain branches of the medical services, a separate industrial service generally being preferred.

In most socialist or communist countries, medical studies are separated into two groups: one concerned with preventive and social medicine, the other with after-care. In some cases, this has been so arranged that doctors in charge of industrial medicine in fact control the health of a whole industrial community and have the right to take any initiative they believe to be necessary.

A more precise understanding of the needs of the worker and of prevention of the more common occupational diseases has been stimulated by international organizations, such as the International Labour Office, or ILO. Thus there exists today a branch of medicine the purpose of which is to try to understand man against the background of his profession, as well as that of his family and social class, in order to find the true causes of his illnesses.

Already, in place of toxicology as such, where the absorption of a known poison gives rise to a group of symptoms as precisely defined as the steps in a demonstration, a complex research programme, known as environmental health medicine, has been established, the aim of which is to anticipate a number of conditions conducive to illness. This branch of medicine deals with the causes of occupational diseases induced by such things as dust, atmospheric conditions, lighting, temperature, radiation, or even human relationships, in all of which anomalies may occur in certain occupations.

Another aspect of the same problem is that of the physiology of work, a concept developed by Chauveau and Marey, which embraces effort, the distribution and rhythm of movement, the worker's attitude towards the problems of his work, and various methods of fighting and preventing fatigue. This study now incorporates industrial psychology, which, inspired by methods of psychological testing, is directed towards vocational choice and personnel selection, as well as towards the psychological reactions of people to their jobs; it also includes the study of training, publicity, and even research into sociological and psychological conditioning.

Occupational diseases

What are known as occupational diseases correspond in practice to greatly differing nosological groups. One such group includes diseases which extend beyond the limits of the occupation concerned (tetanus, for example), but which appear with special frequency among certain workers. Another group comprises rather rare diseases, diagnosed as intoxications, but without certain characteristic symptoms, which also and frequently affect certain categories of workers (such as agranulocytosis in workers handling benzene). Some diseases only attack certain groups of workers

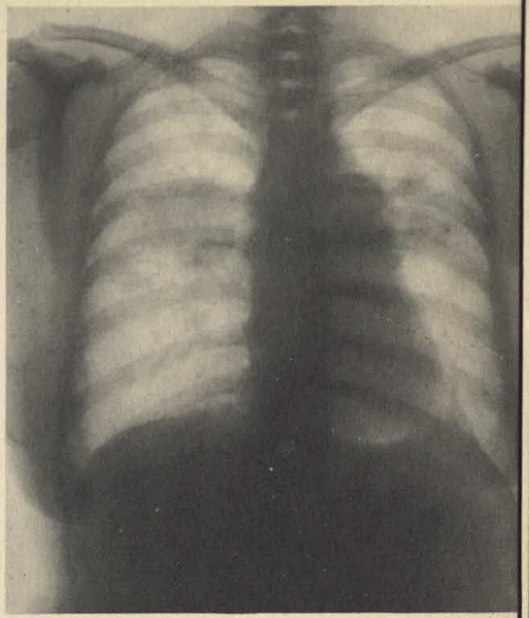


Fig. 2. For a long time, doctors thought that silicosis was a form of tuberculosis. As treatment of this disorder progressed, it was realized that in fact silicosis was caused by silica. The above radiograph shows a case of silicosis without tuberculosis.

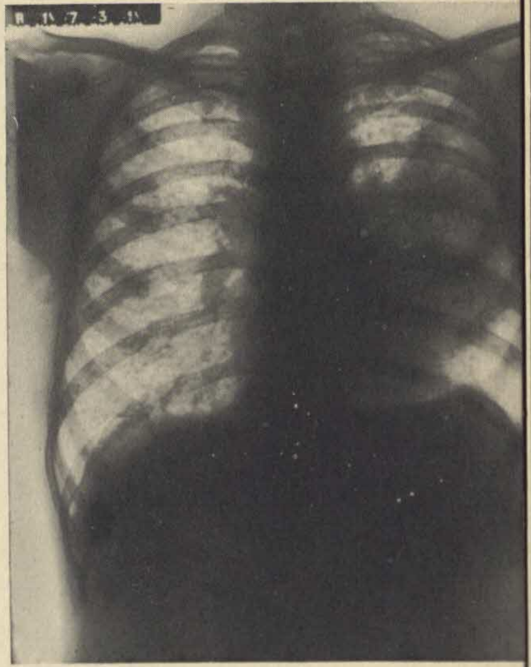
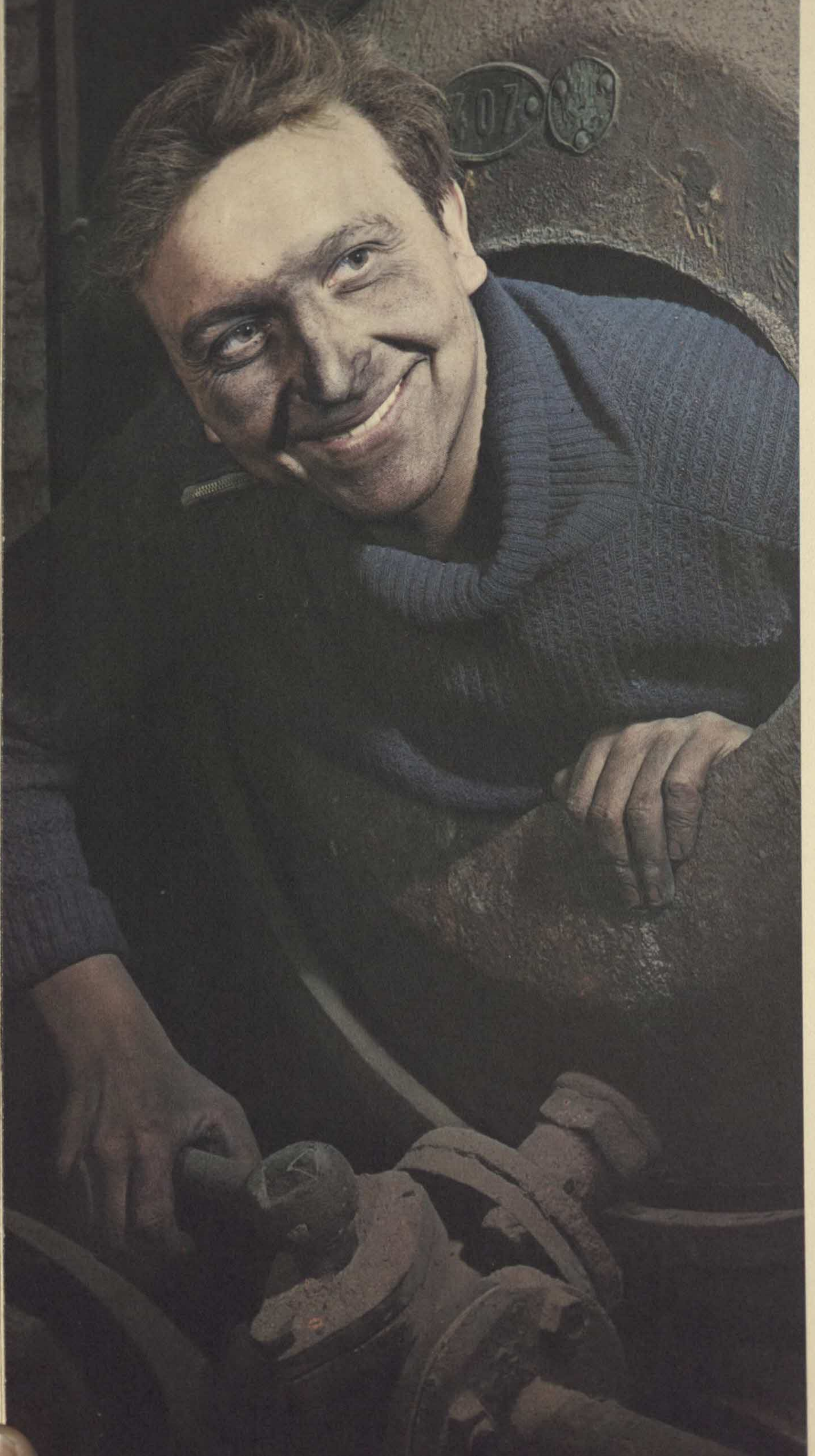
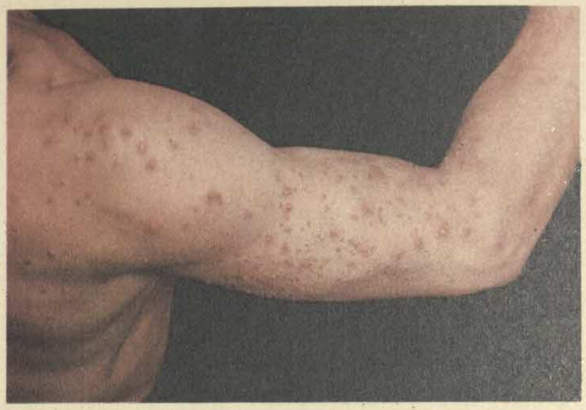


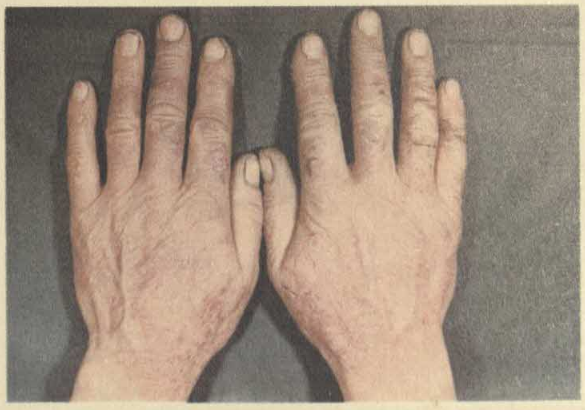
Fig. 3. A case of silicosis associated with tuberculosis; the picture is very different from that of pure silicosis.



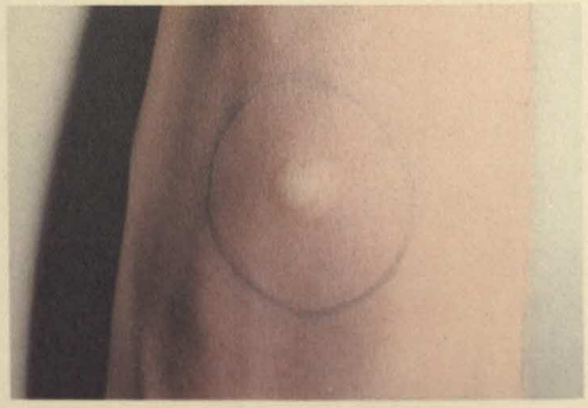
Occupational diseases



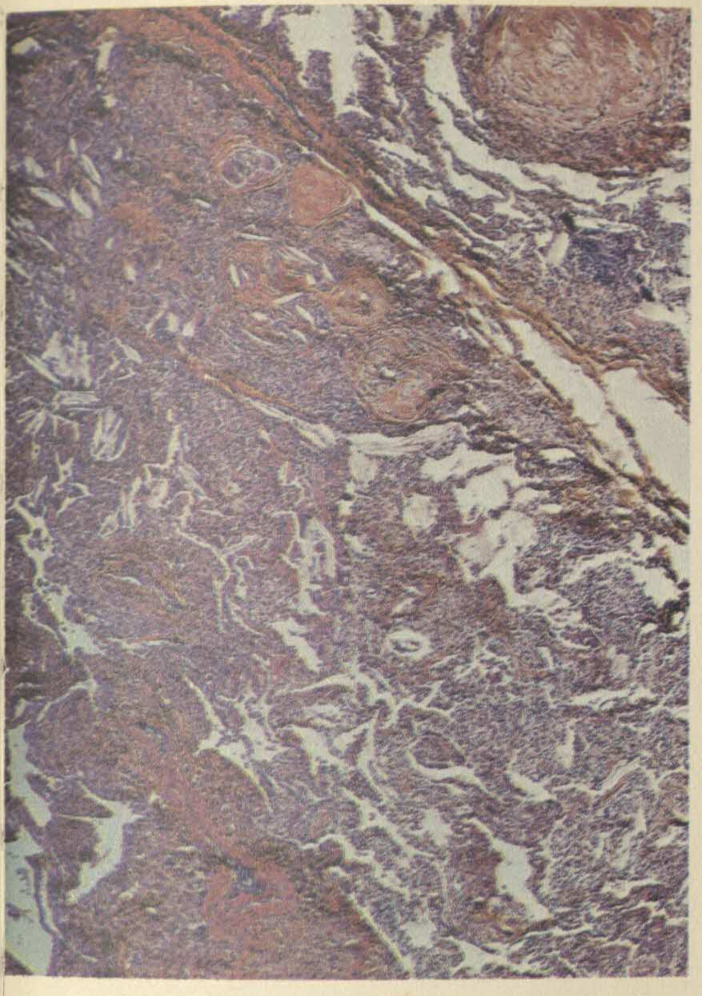
Until the study of cutting oils made effective preventive measures possible, eleoconiosis affected turners and setters. (Photo Dr Fournier).



Eczema of the hands is a strong allergic reaction caused by some chemical substances; it is serious and frequent among industrial workers. (Photo Dr Fournier).

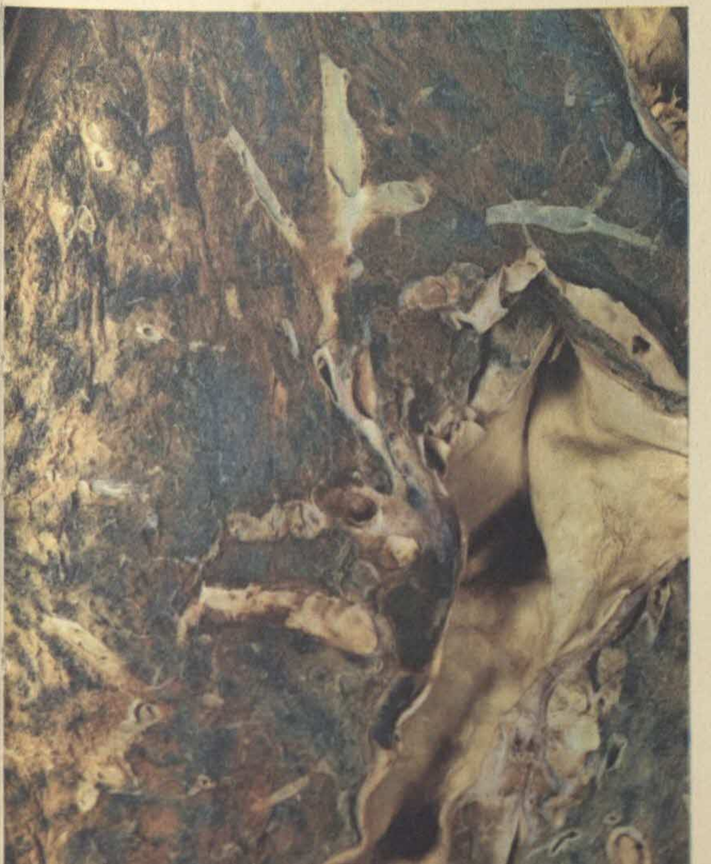


Occupational dermatology has increased considerably among workers whose jobs involve the handling of chemical products. Skin tests (ie, an intradermo-reaction test) are used to identify harmful substances.



We have seen that silicosis may affect workers in a dusty atmosphere. Here we see a section of silicotic lung tissue. (Photo Lod).

High-temperature metal-working is dangerous because it may cause serious eye and skin lesions.



Inflammation of the pulmonary artery (arteritis) caused by repeated inspiration of irritating agents (dusts and chemical substances). (Photo Lod, from the personal museum of Dr Kourilsky, Hôpital Saint-Antoine, Paris).

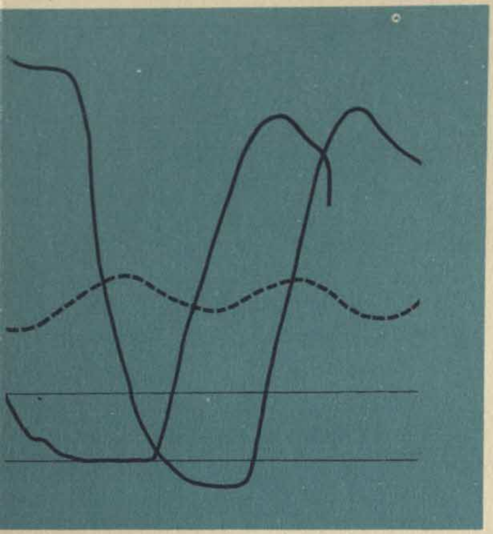


Fig. 4. A simple respiratory test (Tiffeneau's coefficient calculation) shows the modification in speed of expiration after inhalation of an aerosol of a very dilute solution of penicillin. Broken line, normal expiration speed; solid lines, speed of expiration in an asthma sufferer sensitized to penicillin.

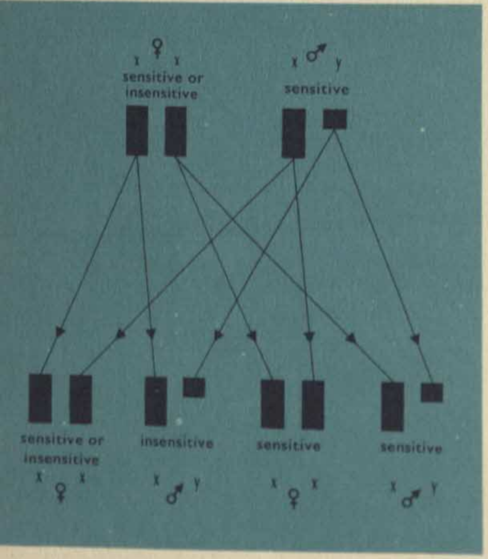


Fig. 5. Malaria, an 'environmental' disease, becomes an occupational disease in certain categories of workers engaged in malarial regions. In certain cases, anti-malaria treatment causes accidents in persons who have a hidden defect; transmission is hereditary, dominant in men.

and 'characterize' the occupation (for example, silicosis, or 'flinty chest' in miners).

Diseases in the first category correspond, in fact, to true working accidents. Such would be the case of a sewerman who contracts spirochaetal rat-bite fever. If the disease has been transmitted by a rat-bite, one may speak of it as an accident; if on the other hand, the contamination is due to sewage, the term occupational disease is to be preferred. Clearly, only statistical frequency can justify such terminology, and specialized studies are limited to examining conditions of work and means of prevention, in this case, the destruction of rats.

The second and especially the third category belong to the particular class of chronic poisoning. But unfortunately the cases to be considered differ from the obvious and clear cases of acute poisoning and present the most diverse and uncertain appearances.

This has reached such a point that French legislation, wishing to simplify matters, has been carried astray. Thus the appearance of a nervous complaint such as Parkinson's disease in a worker in a manganese mine may lead without any other evidence to a diagnosis of extra-pyramidal manganese syndrome. Is this an inappropriate measure? We do not think so. In seeking an equitable solution based on the assessment of coincidences, it was reasonable to embody provisions concerning such a contingency in legislation, since no peremptory argument could show any evidence to the contrary. It is not solely a point of doctrine; all progress in medicine teaches us that, for reasons arising often from ordinary prudence, certain doctors will accept only very definite evidence, whereas others, even very competent doctors, suddenly become enthusiastic about new theories. It is therefore not without point to define an average term of reference in written legislation.

The best proof of this is supplied by silicosis, around which the 'battle of the theorists' raged between partisans of a disease caused by silica and those of tuberculosis greatly modified by silica dust.

In 1961, although the question had been settled in favour of a disease due to contact with silica, a commission of the ILO decided that it would be useful to establish, not a simple list of the clinical forms of silicosis, but a collection of characteristic radiological documents, which have become a kind of catalogue of standard silicosis diseases.

Another aspect of the study of occupational diseases is concerned with ethics. As soon as doctors and biologists have proved the existence of an occupational disease, we are faced with a fundamental problem of ethics: to what extent has one the right to allow a worker to follow a dangerous occupation? The question is a real one and a serious one; it can be resolved neither by an attitude of indifference on the part of the employer who believes that prevention is too costly, nor by an equal indifference on the part of the employee who may find it even more costly to himself to be prevented from earning a high salary because of a hypothetical risk.

The theoretical answer is easy: if the disease is a benign one, and really does not menace either the life of the worker or his mode of living, correct supervision and suitable measures of prevention will be sufficient. At most, if the inconveniences of the occupation (such, for instance, as respiratory or skin allergies) become a very heavy handicap, a change of work and a compensatory payment would seem reasonable.

On the other hand, it is scandalous that there should still be risks of poisoning affecting vital organs and involving the worker in taking chances that may have irremediable consequences.

Thus poisoning of the haematopoetic system, such as that caused by benzene, which can cause dangerous illnesses like agranulocytosis, a poison affecting the nervous system, such as methyl bromide, or a liver poison, such as tetrochlorethane, should be strictly eliminated from industry—and here there is wide scope for applied research. Alternatively, such poisons should be handled only in fully automated factories, as in plutonium plants, where highly toxic radioactive substances are used. However, a dogmatic attitude does not always correspond to practical technological needs, and the fact that cases are seldom seen in which poisoning is indisputably the cause, leads one to recommend a great deal of care and vigilance.

Recently, a memorandum from the ILO mentioned some hitherto unexplained cases of death which have been linked, through studies made in many laboratories, with metabolic poisoning caused by pentachlorphenol, a substance used in the treatment of timber, the toxicity of which had been little known until then. Here is a clear example of what can be done by international collaboration. We are gradually establishing a medical classification of poisons and toxic agents which supersedes a merely physical or chemical classification.

This older type of classification is retained in French law in the tables of compensation for occupational diseases. It needs to be supplemented by a list of toxic substances that cause working accidents, as well as by a list of occupational diseases not specified as due to poisons (cyanides, carbon monoxide, etc—their number is unlimited), or to physical agents (electricity, electromagnetic waves), and to bacterial, parasitic and viral infections (tuberculosis in sanatorium nurses, malaria in technicians sent to endemic areas, etc).

Conversely, to list toxic substances according to the main symptoms observed is not easy, as an example will show. The 15th Table concerns aniline and its homologues and many aromatic amine near-derivatives. Among the occupational diseases mentioned are: 'acute accidents' (nervous manifestations with cyanosis), anaemia with cyanosis, and subicteris, acute, relapsing or chronic dermatoses, acute haemorrhagic cystitis, vesicle lesions (bladder congestion with varicosities, benign tumours, malignant tumours) confirmed by cystoscopy.[1] In practice, this unsystematic nomenclature means, in the case of 'acute accidents', special toxic manifestations due to the transformation of blood pigment into methaemoglobin. These intoxications, generally of a benign nature and followed by recovery in a few hours, are sometimes fatal owing to asphyxia. Haemolytic anaemia with methaemoglobinaemia is usually curable in a few weeks; cutaneous accidents caused by sensitization may take a very long time to cure, if the sensitized worker is not moved from his job, but they are not dangerous; bladder troubles are due to simple congestion, or to tumours resulting from chronic poisoning, sometimes benign but sometimes malignant, and which may lead to death. Moreover, what appears to be a benign symptom does not necessarily mean that after a few years the worker will not have a bladder cancer. The only means of control has already been mentioned; it consists of a painful examination by cystoscopy, which must be repeated if supervision is to be efficient.

In conclusion, we must repeat that the most diverse organs may be attacked by chronic poisoning and that up to now it has been very difficult to foresee, even approximately, the possible harmfulness of a new product. Recently 'epoxy' derivatives were shown by experiment to be toxic to the haematopoetic system. A new potential danger was thus reported, and years of study will still be necessary to confirm or reject the deadly effects which these industrial products can have on man.

TABLE OF OCCUPATIONAL DISEASES

PARASITES AND MICROBES

- Parasites
  - *Hookworm*
- Microbes
  - *Tetanus*
  - *Ictero-haemorrhagic spirochaetosis*
  - *Leptospirosis*
  - *Brucellosis*
  - *Anthrax*
  - *Bovine tuberculosis*
  - *Tularaemia*

MINERAL AGENTS

- Chemical elements
  - *Arsenic*
  - *Beryllium*
  - *Chromium*
  - *Mercury*
  - *Manganese*
  - *Nickel*
  - *Phosphorus*
  - *Lead*
  - *Sulphur*
- Others
  - *Cements*
  - *Alumino-silicates of calcium*

ORGANIC AGENTS

- Halogenated aliphatic hydrocarbons
  - *Methyl bromide*
  - *Methyl chloride*
  - *Carbon tetrachloride*
- Aromatic hydrocarbons
  - *Benzene*
  - *Benzol*
- Nitrate aromatic hydrocarbons
  - *Dinitrophenol*
- Amino aromatic hydrocarbons
  - *Aniline*
  - *Naphthylamine*
- Hydrazines
- Others
  - *Lubricants*
  - *Tars*

PHYSICAL AGENTS

- Ionizing radiations
  - *X-rays*
  - *Radioactive substances*
  - *Sources of particle-emission*
- Pressure
  - *Pneumatic hammers*
  - *Atmospheric pressure*

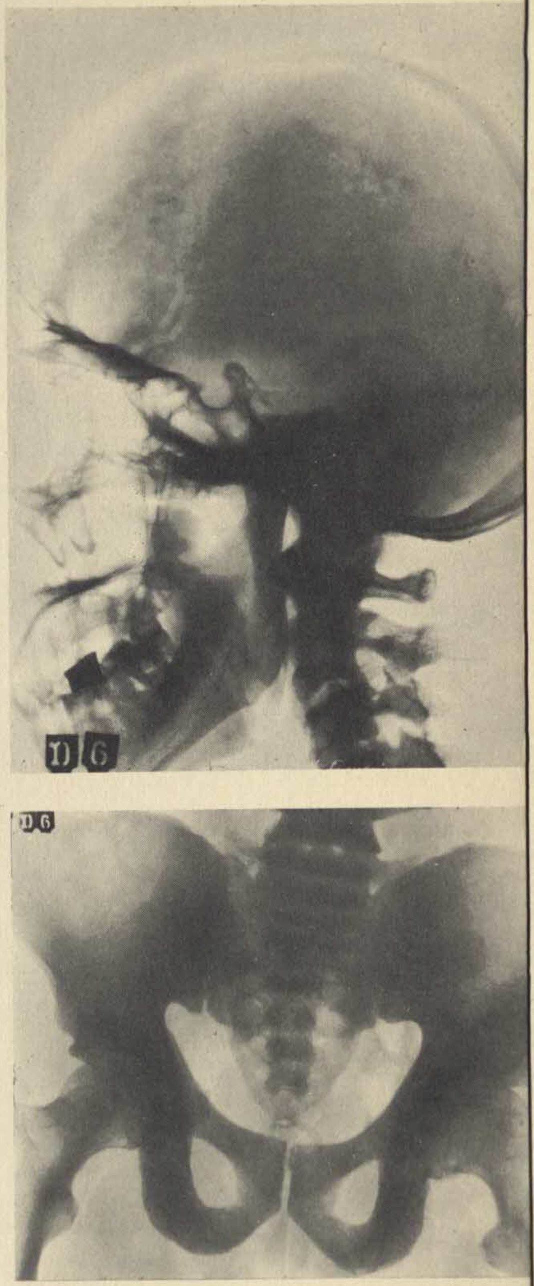


Fig. 6. Twenty-five years' working with cryolite, used in aluminium production, causes an abnormal calcification of the bone, the periosteum, and certain tendinous insertions. This fluorescent osteopetrosis is shown in these two radiographs.

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(1) Cystoscopy: *Endoscopic examination through natural openings permitting observation of the cavity of the bladder.*

Alcoholism

Michel GAULTIER

Alcoholic intoxication can have the most serious biological consequences for a man and his children. To this danger must be added social consequences: a lowering of business efficiency, frequency of industrial accidents, and broken homes. Dr Gaultier here describes the pathological aspects of this menace, as well as the possibilities for present-day and future treatment. Although his remarks are based largely on facts and figures derived from experience of the problem of alcoholism in France, in general it may be said that his conclusions are applicable both to individual sufferers elsewhere and all communities in which there is an unduly high rate of alcoholic consumption.

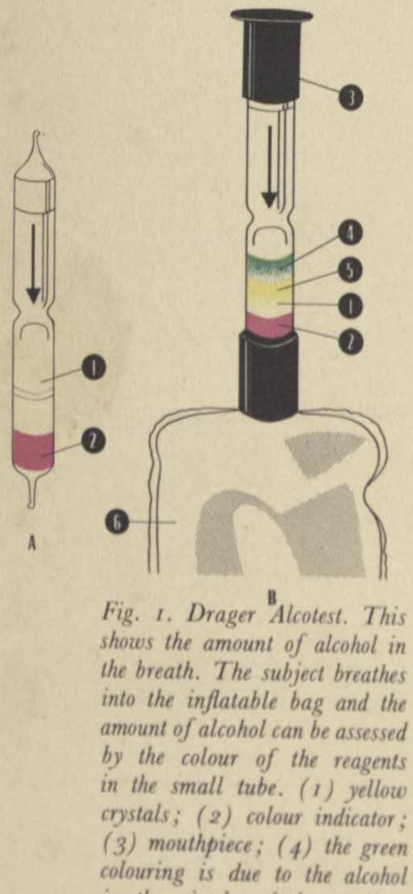


Fig. 1. Drager Alcotest. This shows the amount of alcohol in the breath. The subject breathes into the inflatable bag and the amount of alcohol can be assessed by the colour of the reagents in the small tube. (1) yellow crystals; (2) colour indicator; (3) mouthpiece; (4) the green colouring is due to the alcohol in the air breathed out (here more than 0·8 per 1,000); (5) yellow ring; (6) inflatable bag. (Reproduced from Lessons on Alcoholism *by Dr Jean Lereboullet, 1959.)*

When considering this subject, we must bear in mind its two complementary, individual and social aspects—drunkenness and the highly complex consequences of prolonged intoxication—both of which give rise to serious problems.

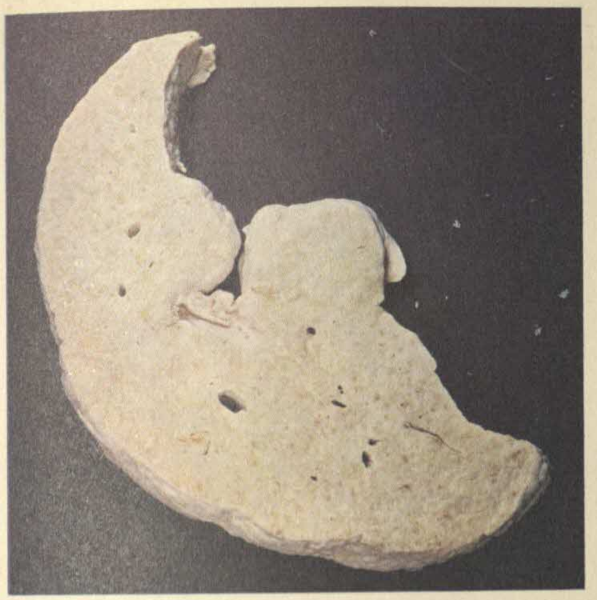
The individual aspect

The absorption of alcohol in the form of a concentrated solution, whether sweetened or not, always leads to the same result after a certain amount has been taken: a state of drunkenness. The distribution of alcohol in the blood and organs after it has been drunk is well known: it can be seen to be evenly spread in most of the tissues, except the liver. Alcoholaemia[1] rises for a period of an hour and a half, when it reaches its maximum. It then subsides rapidly, following a smooth linear curve. Elimination in the urine and through the skin is very slight. Respiratory elimination in proportion to the rate of alcohol intake has led to the development of an alcohol test carried out by means of the measurement of ethanol in the air breathed out by the drinker (breathyliser). Altogether, excretion accounts for not much more than 10 per cent of the amount taken. The entire biological problem presented by alcoholism is therefore to be found in the breakdown which it undergoes in one organ, the liver. The liver is rich in alcohol dehydrogenase, whose action results in the formation of ethanol which, through the action of xanthine-oxydase leads in its turn to the formation of acetic acid. A very small amount of alcohol is enough to saturate these enzymes, which explains the regular destruction of alcohol that Widmark has called the coefficient of ethyloxidation. This coefficient is as follows, measured in milligrams per minute: 2·5 + 0·56 for men, and 2·6 + 0·37 for women. According to other research workers, variations are perhaps even more marked.

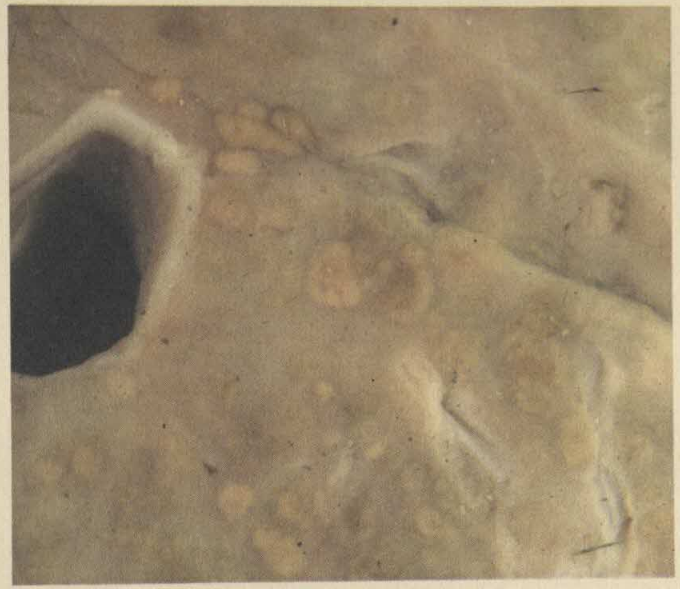
The maximum level of alcoholic intoxication varies, in fact, in a very important manner with diet. According to Goldberg, a large meal, the dilution of an alcoholic drink, or the richness of the meal in sugar and protein, could lead to a maximum of concentration varying from 30 per cent to 70 per cent. On the other hand, after absorption of a concentrated alcohol, alcoholic intoxication would be at a maximum.

In medico-legal terms, there are three stages in the study of a state of drunkenness: non-medical observation by a police officer, medical and clinical examination, and measurement of the amount of alcoholic intoxication.

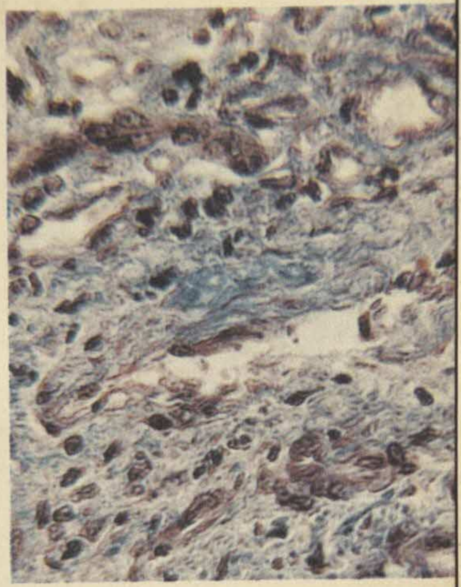
The first two methods are used in trying to detect functional signs, ie, the state of the breath, flushing of the face, word slurring, uncertain movements, staggering walk and spontaneous nystagmus.[2] Semi-clinical examinations, consisting mainly of tests of steadiness



General view of a lobe of a cirrhotic liver. The liver nodules (see following photographs) have been attacked by fatty degeneration, causing them to become yellow. They are surrounded by an area of sclerotic damage.



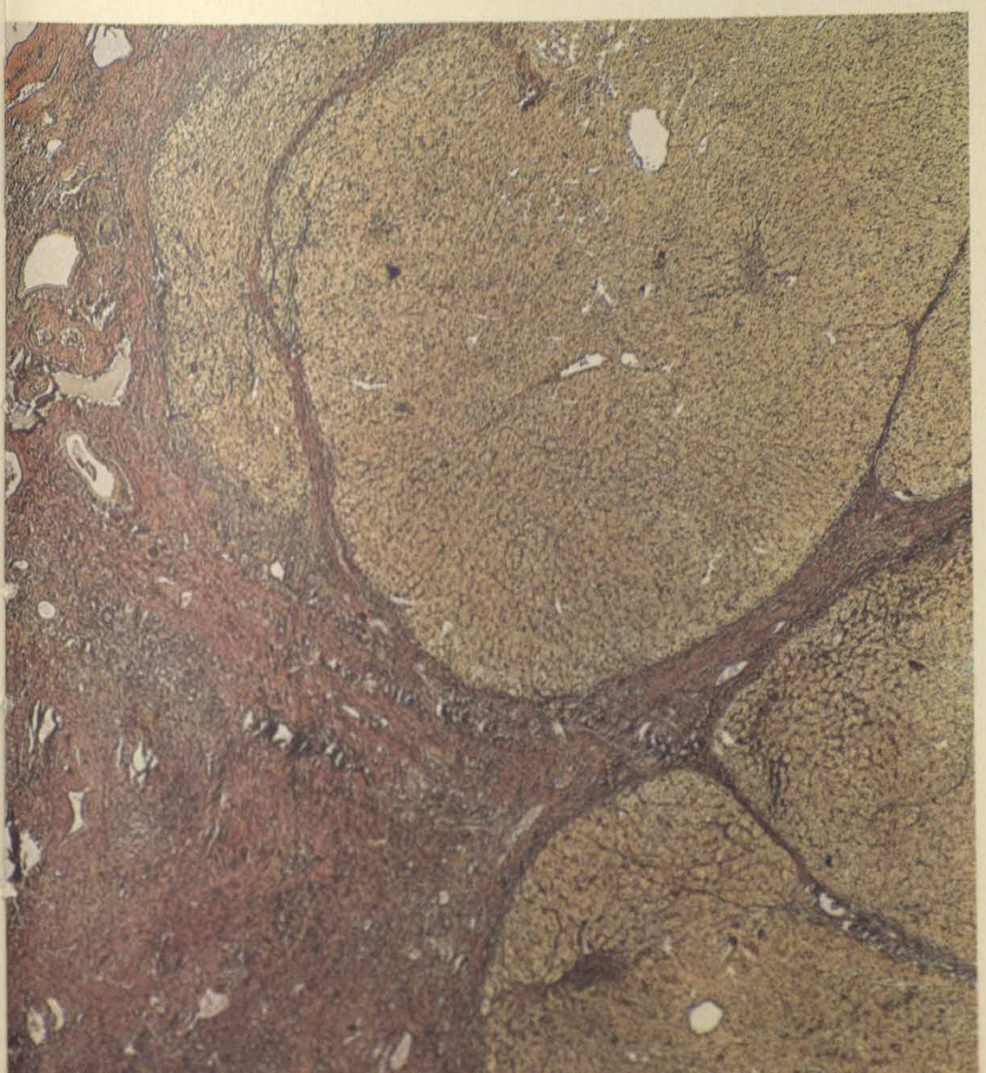
Detail of the structure of a nodule; the fatty degeneration of the cells is clearly visible. On the left can be seen part of a dilated hepatic vein.

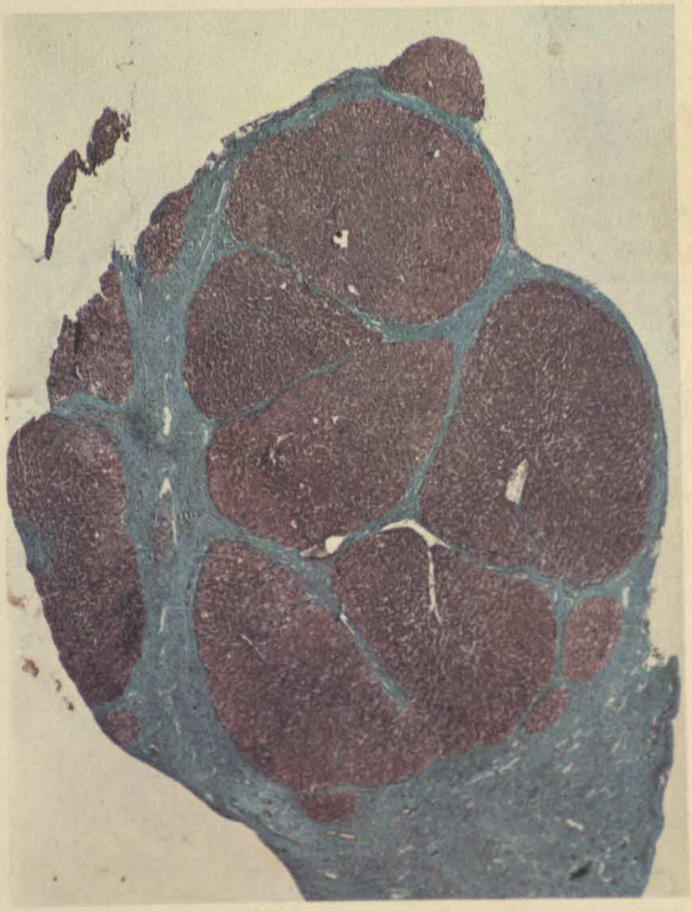


Detail of sclerotic area; the normal hepatic cells have been destroyed and surrounded by collagen fibres (stained dark blue).

Cirrhosis of the liver

Detail and general view of cirrhotic nodules. By a special method of staining, it is possible to note different stages in the progress of cirrhosis. Old collagen fibres are stained red, young fibres greeny-blue.





and alertness, will complement these observations. As distinct from the nuances of clinical examination, the alcoholic intoxication test gives a precise answer that is nearly a hundred per cent accurate. How far can the two approaches be reconciled? The studies made by Goldberg and Moureau have shown that the sensitivity of psychological tests varies considerably, depending on who is being tested, whether it be an occasional drinker, a moderate drinker, or a heavy drinker. As a rule, sensitive tests clearly show up disturbances in occasional drinkers after consumption of approximately 0·50 grams to a pint and three quarters, and in the other two groups of drinkers after consumption of 1 gram to a pint and three quarters. For cruder tests, such as those of balance and obvious states of drunkenness, the figures follow an S-shaped curve which shows that certain people are in a state of drunkenness after having taken one gram to a pint and three quarters; a very small number of people show no comparable anomalies of behaviour when they have taken amounts ranging from 2 to 2·50 grams to a pint and three quarters.

If drunkenness by itself does not lead regularly to definite disturbances of individual behaviour, the same cannot be said when the habit of intemperance is continued for twenty years or so. In this case, dietary disturbances preponderate, accounting for certain very serious complications, such as cirrhosis of the liver (which I shall describe later), alcoholic polyneuritis, and acute cerebral afflictions, often very serious, despite the administration of strong doses of vitamins. Peculiarities of behaviour can become more and more distressing, leading to states of alcoholic rage, dangerous aggressiveness, chronic hallucinations, alcoholic dementia, and delirium tremens with agitation and characteristic hallucinations, accompanied by fever and trembling, which can break out under conditions of sudden disturbance, such as poisoning or infection, or an accident. The life of the chronic alcoholic is menaced; and because of progressive deterioration, he will succumb to a rapid process of ageing, as is shown by statistics.

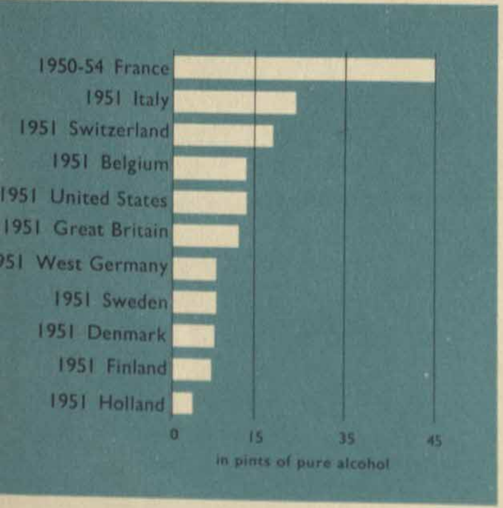


Fig. 2. Total consumption of pure alcohol per adult per year in France and other countries. (From the French National Institute of Demographic Studies, 072–56.)

The sociology of alcoholism in France

France is almost the only country in the world where it is possible to make wide statistical surveys of alcoholism. The principal drink of the population is wine, of which the annual consumption is about 1,980 million gallons (with some recent fluctuations); consumption of pure alcohol in France reached about 220 million gallons before 1939, but this figure has since declined. Allowing for the fact that the consumption of alcohol before the age of twenty is low, individual consumption still remains fairly high and that of pure alcohol before the last war reached as much as 8 gallons per adult per annum.

A clear difference is apparent between men and women; the death rate for men of between thirty-five and sixty is nearly three times as great as that among women, and herein lies one of the most important reasons for the difference in the survival rate of men and women.

Cirrhosis is very well known in every country: it is a fairly rare disease which is observed after viral hepatitis and certain exceptional cases of poisoning; it does not often occur, except in countries where there is chronic under-nourishment (as in some African countries, for example). As regards countries where nutrition is normal and abundant, it occurs chiefly in France. A recent study by the World Health Organisation, based on statistics from a Paris hospital, has shown that people suffering from cirrhosis are nearly always found among those who drink more than five and a quarter pints of wine a day over a period of many years (on an average, fifteen to twenty).

The basic disturbance occurs in the diet, since alcohol itself is not particularly poisonous to the liver, as long as it does not become linked with direct poisoning of the liver cells. Experiments have shown that the dietary regime of an alcoholic is extremely damaging to the liver, as the alcohol intake forces the body to function in a permanent state of imbalance, with a preponderance of acid radicals at the cost of a considerable consumption of certain nucleotides and water-soluble vitamins; but the alcoholic, who spends a large part of his income on drink, will tend to buy the least expensive forms of foods, such as bread, sugar and potatoes. He rejects—because he cannot afford it—a balanced diet based on fish, cheese, fruit and milk.

Alcoholism is the real cause of the nutritional pathology of the French, which explains a comparison to be made between the type of cirrhosis in France and that due to protein deficiency. It is hardly necessary to emphasize the seriousness of alcoholic cirrhosis and the

(1) *Alcoholaemia: presence of alcohol in the blood.*

(2) *Nystagmus: oscillatory, brief and jerky eye-movements, usually indicating a lesion of the cerebellum, but also to be seen in alcoholics and mongoloid children.*

cost of treatment, which includes high doses of amino acids, vitamins and proteins, and possibly even the use of life-saving and resuscitation equipment.

Prophylaxis and prevention

For several years, a series of studies have been focused on the psychological aspect of alcoholism and the reasons that impel a patient towards a state that can be dangerous both to himself and those around him. Psychiatrists and psychologists who have studied these syndromes have divided alcoholics into two large groups, according to whether a well-defined psychiatric syndrome existed before the patient became an alcoholic or not. Neuro-psychiatric syndromes mean principally states of depression coming in cycles, in which the patient, often incapable of action, finds alcohol a sedative, a means of oblivion, and above all a subjective alleviation of his troubles. Many people in asthenic conditions turn to alcohol regularly in their struggle against obsessive thoughts of failure, inadequacy, or violence. Moreover, it is not unusual to find that fairly well-defined character defects, whether or not they are secondary to some forms of encephalitis, or associated with debility, paranoid behaviour, or epilepsy, lead to chronic alcoholism. Alcoholism can also play a part in the anti-social behaviour of certain perverts, whose psychiatric classification is an extremely difficult problem.

In the absence of an obvious psychiatric disorder, there still remain certain fundamental causes of maladjustment, among which matrimonial difficulties seem to preponderate. Some research has established that alcoholism frequently starts after the first few years of married life, following disturbances of varying importance: quarrels, adultery, difficulties of life with numerous children, domineering wives who are often older than their husbands, who become alcoholics, changes of job, inability to adapt oneself to a job carrying greater responsibility, accidents at work, unemployment—all these are indications of the successive emotional disturbances which, little by little, can lead to a complete maladjustment.

However, in France, at any rate, alcoholism is far more a way of life, or a collective contamination, than a true addiction or symptom of maladjustment. The temptation provided by friends, factory or workshop, and by the retail wine shops that are near every centre of work and of leisure activity—and often the extremely tolerant attitude of women, are responsible for the great number of alcoholics. The problem of preventing alcoholism always comes up against the fact that alcoholics are generally normal, or nearly so, right up to the phase of serious poisoning, with accompanying deterioration of mental powers. Because of this normality, there frequently occur symptoms of dangerous involuntary behaviour in otherwise apparently harmless situations: careless driving and carelessness about safety precautions. The outcome is a high death-rate resulting from industrial and road accidents.

It is almost impossible to treat acute drunkenness because there is no substance which will accelerate the elimination of alcohol. Nevertheless, administration of sugar, or of medicine to keep the patient alert, will prevent certain rare complications from occurring.

Among the very serious conditions which have benefited from recent therapeutic discoveries is delirium tremens which, thanks to antibiotics and to rehydration and rechloridation, can often be brought under control by certain steroid tranquillizers and by chemical substances that affect acute disturbances. Since these discoveries, the death rate for delirium tremens has been considerably reduced.

The greatest efforts to prevent alcoholism should be directed towards the temptations that lead people to become alcoholics. Many alcoholics are intelligent enough to understand the dangers of alcoholism and struggle to rid themselves of their habits. In these cases, such measures can be taken as the apomorphine cure, now hardly used at all, and 'preventive methods', consisting of doses of 'antabuse' tetra-ethylthiuram-disulphide, which produces a painful nitritoid syndrome when alcohol is drunk. This treatment is dangerous for alcoholics of low intelligence, who may continue to drink, and accordingly to risk serious complications. The treatment cannot be applied in cases of serious liver and kidney complaints. Results of this treatment have only been moderately successful, and where it has been given to all comers, the number of failures has reached 80 per cent.

The problem of alcoholism cannot therefore be solved by doctors. All they can do is to point out to the public authorities the danger of the present situation, the inadequacies of the law, and, leaving aside all considerations of demagogism, the severity of the measures of enforcement which should be the prelude to establishing effective legislation.

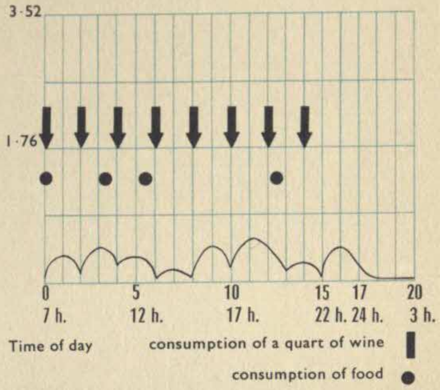
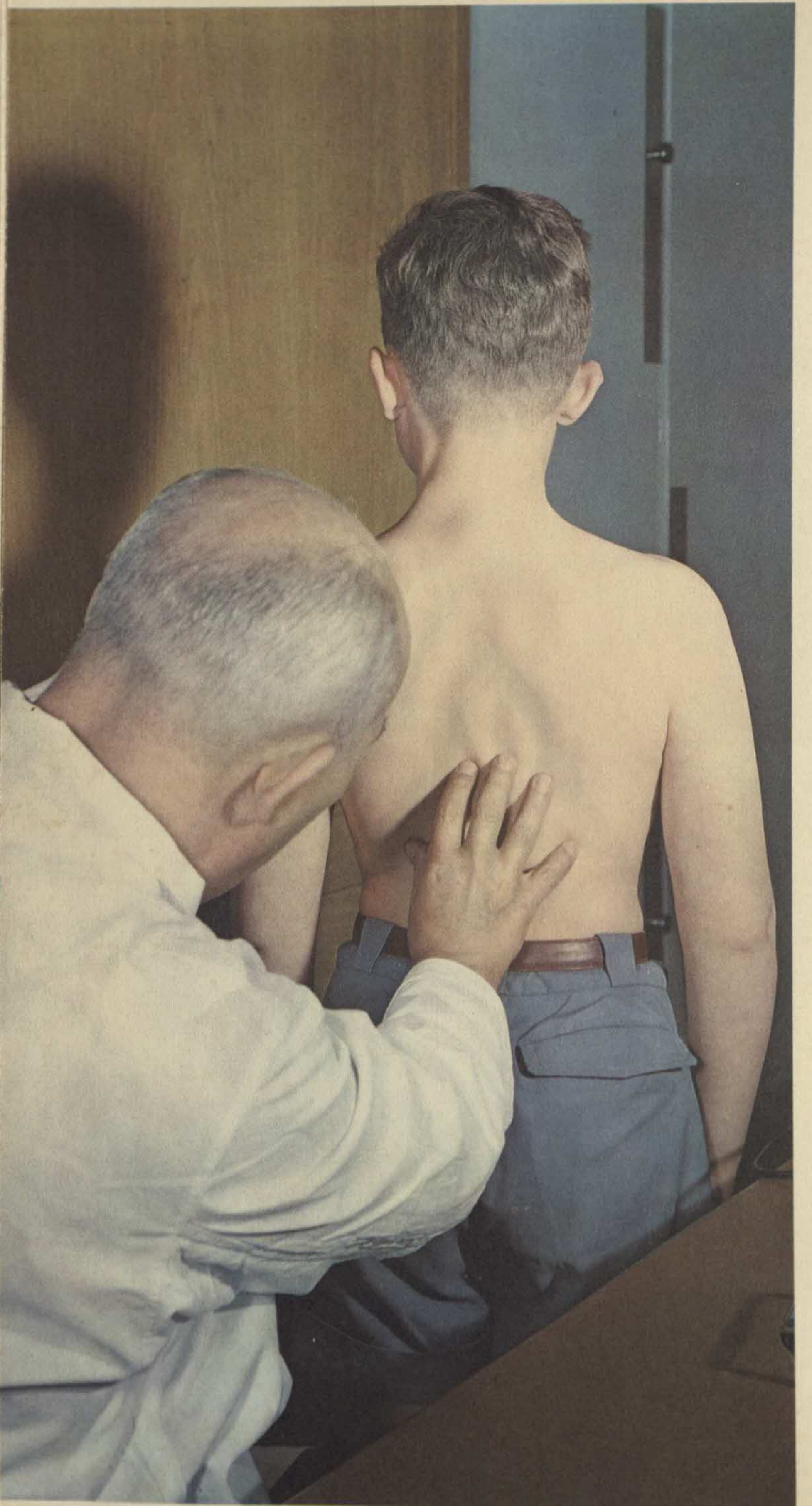
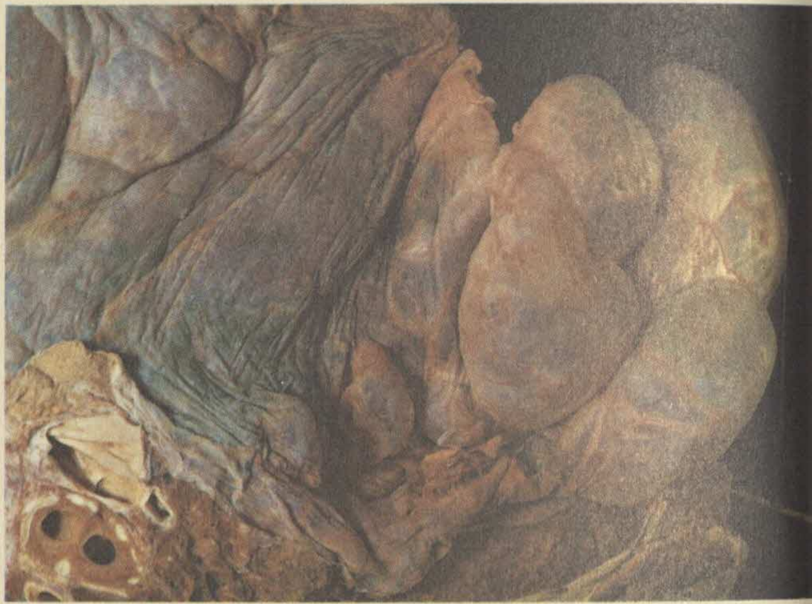
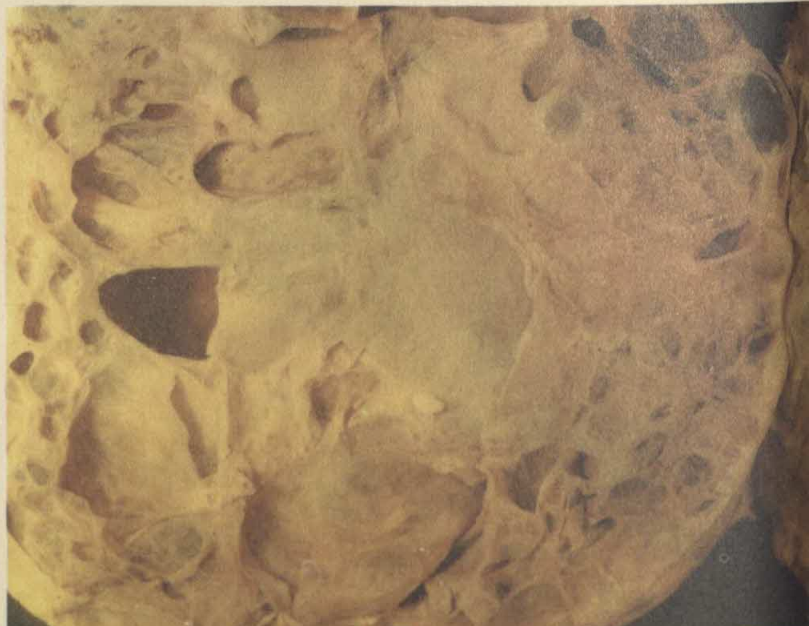


Fig. 3. Graph showing the amount of alcohol in the blood after consumption of approximately three and a half pints of wine on an empty stomach; 0·24 pint every two hours; (based on figures supplied by the French National Institute of Demographic Studies, 053·55).



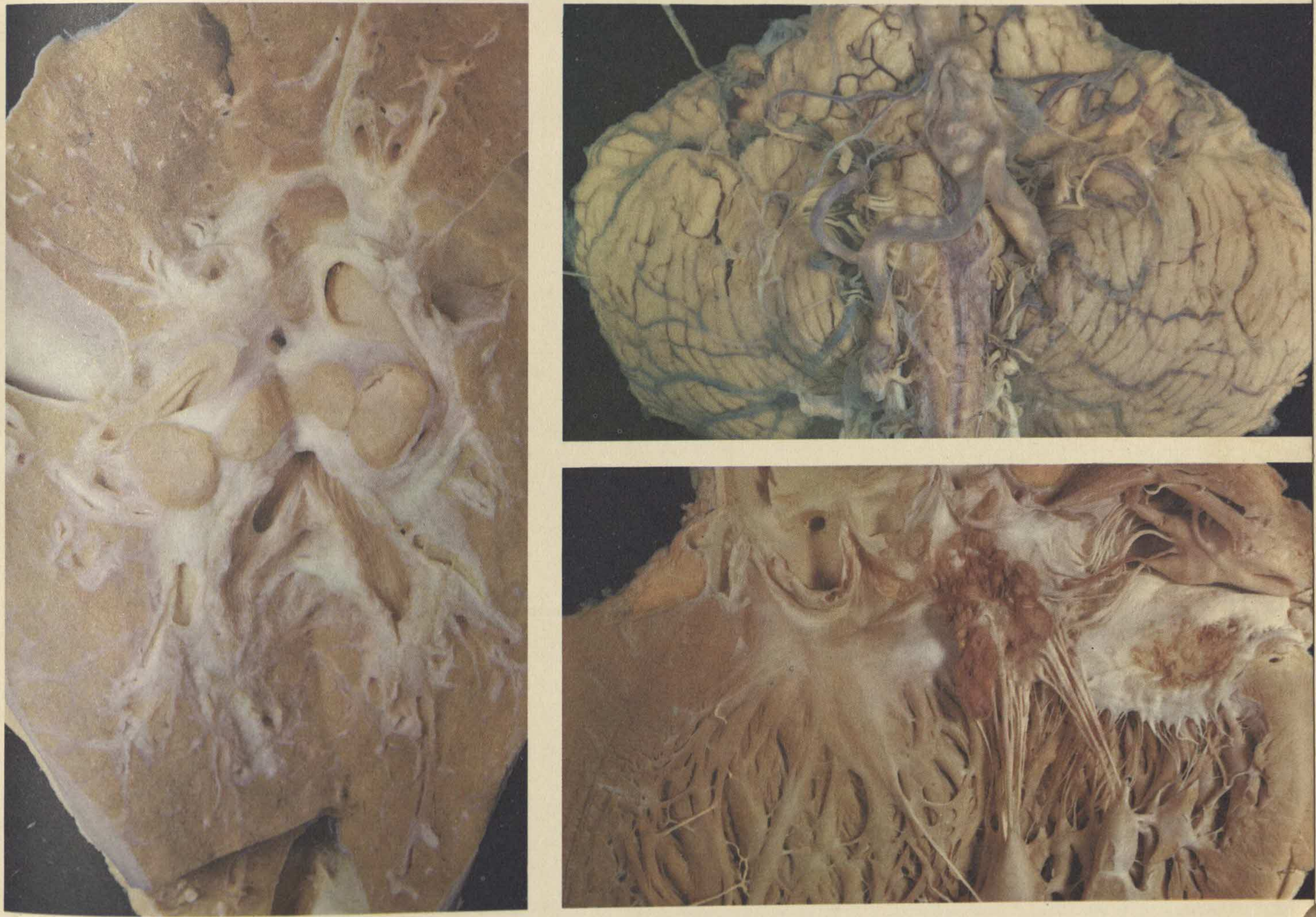
PART TWO





In this second section, we shall outline a series of diseases that are acquired or congenital, reversible or irreversible, and reach all major parts of the human organism. These lesions of internal function are as numerous as, and often more serious than microbial diseases. These photographs, taken in Professor Kourilsky's museum, show a number

Disorders of internal function



of organs the malformations of which can seldom be cured by surgery or modern treatment. From top to bottom and from left to right are shown a cyst of the upper lobe of the lung, a renal cyst (a congenital malformation that is slowly but progressively irreversible), lung tuberculosis in a child (a reversible disease), an aneurism of one of the brain arteries (incurable) and an ulcerous lesion of the endocardium (always amenable to antibiotic treatment, though the sequelae of the lesion itself sometimes require surgical intervention).

The anaemias

Ruggero CEPPELLINI and Claude JACQUILLAT

When they speak of anaemia, doctors mean the condition of a person who has less than the normal amount of haemoglobin. Anaemia is not, as many people think, synonymous with a diminution in the number of red cells. There are some anaemias in which the number of red cells per cubic millimetre of blood is normal, though each of them contains less than the proper amount of haemoglobin; we speak of normochromic, hyperchromic, and hypochromic anaemia, according to the relationship between the amount of haemoglobin and the number of red cells per unit volume of blood. Haemolytic anaemia results from the destruction of red cells.

All anaemias have certain symptoms in common, resulting directly from a deficiency of haemoglobin,[1] which reduces the blood's ability to carry oxygen from the lungs to the rest of the body. This results in the whole organism being permanently in a state of slight anoxia. The symptoms of anaemia are: pallor of the skin and mucous membranes (lips, conjunctivae, etc); general lassitude; palpitations; breathlessness on slight exertion; buzzing in the ears; a tendency to faint, etc. Their severity is in direct proportion to the degree of anaemia.

Pernicious anaemia

True pernicious anaemia attacks men and women alike between the ages of thirty and sixty. It occurs throughout the world, but is more common in the Anglo-Saxon than in the Latin and Slav races.

At first, the disease reveals itself insidiously. The first signs nearly always appear in the digestive system: loss of appetite, indigestion, a burning sensation in the mouth; then the tongue becomes red, dry and smooth and loses its papillae. These symptoms are usually disregarded because the increasing lassitude and loss of appetite are almost imperceptible; even the pallor may pass unnoticed until it becomes very marked. Because these symptoms are only gradual, doctors usually do not see the disease in its early stages, but only when the pallor is striking, with a slightly yellow tinge, like old ivory. On examination of the blood, the haemoglobin and red-cell count will be found to be much reduced, perhaps to 20 per cent of the normal. In the bone marrow, characteristic large cells (megaloblasts) will be found; these are derived from the normoblasts that normally give rise to red blood cells. The microscopic appearance of the sternal bone marrow is so typical that this alone makes it possible to diagnose pernicious anaemia. Another characteristic feature is achlorhydria.[2]

The clinical picture may be complicated by nervous symptoms, such as paraesthesiae of the hands and feet (tingling, feelings of heat and cold, etc). At a later stage, there may also be difficulty in holding objects, unsteadiness on the feet, disturbances of muscle tone, and occasionally paralysis or mental disorder.

The natural course of pernicious anaemia is slow and periods of spontaneous improvement alternate with periods of deterioration. The outcome in earlier days was invariably fatal, the illness lasting from six months to several years; but the outlook has been completely altered by the introduction of liver extracts and vitamin B_{12}.

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[1] Haemoglobin, *a red compound of protein and iron, is the respiratory pigment of the blood. Its function is closely connected with the presence of iron in its molecule. Haemoglobin is, in fact, formed by the combination of a globin, a protein rich in amino acids, with a coloured substance containing iron and four pyrrole rings. Owing to their haemoglobin, the red cells of the blood are able to take up oxygen from the air and yield it back to the tissues. One gram of haemoglobin contains 0·34 gram of iron.*

[2] Achlorhydria or anachlorhydria: *absence of hydrochloric acid and digestive enzymes from the gastric juices.*

The cause of pernicious anaemia is the absence in the gastric juices of a substance known as 'intrinsic factor', the function of which is to facilitate the absorption of vitamin B_{12}, which is necessary for the normal development of red blood cells in the bone marrow.[3] Without this intrinsic factor, the vitamin cannot be assimilated, even if there is enough of it[4] in the food.

With treatment, the anaemia rapidly improves and the nervous symptoms disappear. Treatment, which consists of intramuscular injection of liver extract and vitamin B_{12}, must be kept up for the rest of the patient's life in order to prevent a relapse.

The other forms of hyperchromic anaemia are similar to pernicious anaemia, but arise from different causes. *Bothriocephalus* infestation occurs in some people because they harbour an intestinal parasite called *Diphyllobothrium latum*; this looks rather like the tape-worm, *Taenia saginata*.[5]

This form of anaemia is very common in countries bordering the Baltic Sea (particularly Finland), where it affects about 25 per cent of the population, and also in certain cantons of Switzerland, in Japan, and round the Great Lakes of North America. The infection is contracted by eating fish containing the larvae, which develop into adult worms when they reach the intestine. The worm has a great avidity for vitamin B_{12}, which it consumes at the expense of the host. Treatment consists of first eliminating the parasite and then correcting the anaemia with vitamin B_{12}.

The anaemia of *pregnancy*, which is very rare, appears during the latter half of the pregnancy, usually during the last three months. The symptoms are those of any other anaemia, except that there is also a persistent fever, which may suggest the presence of septicaemia. Before the discovery of liver extract treatment, death occurred in about 90 per cent of cases; but with modern treatment (liver extract, vitamin B_{12}, folic acid) the outlook is favourable. This 'pernicious' type of pregnancy anaemia must not be confused with the common hypochromic form, which is not serious and from which the patient spontaneously recovers.

There is a third type of 'pernicious' anaemia, which may occur after gastrectomy. Patients who have undergone this operation, particularly if a large part of the stomach has been removed, sometimes develop a pernicious type of anaemia. There is little doubt that the cause of this is the consequent diminution or disappearance of hydrochloric acid and of the intrinsic factor.

Hypochromic anaemia

Idiopathic hypochromic anaemia affects only women between the ages of twenty and fifty. Although it has been observed in Chinese and Negroes, the disease occurs most often in the Anglo-Saxon and Nordic races. As in pernicious anaemia, it begins very insidiously; by the time the patient decides to consult a doctor, she has usually had the disease for eight or ten years. The symptoms include loss of appetite, slight nausea, and a sensation of fullness after meals, as well as the symptoms common to all anaemias (weakness, lassitude, giddiness, etc). The skin is pale and greyish; the fatty layer[6] beneath it is somewhat diminished, but there is no actual emaciation.

Examination of the mouth is very important in diagnosing the disease. Usually the teeth are in a very bad state (caries, pyorrhoea, etc) and the patient complains that eating is painful, particularly to the tongue. Another typical feature is fissuring at the corners of the mouth. The cracks are deep and very painful, and resistant to all treatment, except that which cures the anaemia—the ingestion of iron. The patient's hair loses its lustre and becomes rough, coarse and prematurely grey; the nails are thin, brittle and ridged, with elevated edges, making them concave (koilonychia). Menstruation is little affected, but pregnancy considerably aggravates the anaemia, so that the patients often date their illness from a previous pregnancy.

On examination of the blood, the number of red cells is found to be not greatly reduced; indeed, there are often as many as 4·5 to 5 million per cubic millimetre. The haemoglobin content, however, is greatly reduced—perhaps to only 30 per cent of normal—giving the cells a pale appearance (hypochromia). The iron content of the blood (serum iron) is also considerably diminished.[7]

Idiopathic hypochromic anaemia runs a chronic course without any tendency to spontaneous recovery. The patient's gastric juice contains no hydrochloric acid, which is essential for the absorption of iron. Provided iron is given in sufficient quantities, however, the outlook is favourable. The oral route is effective, although iron may be poorly tolerated and insufficiently absorbed by patients suffering from this type of anaemia.

The hypochromic anaemia of ankylosto-

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(3) Vitamin B_{12} *is essential, but only in very small quantities, of the order of a millionth of a gram.*

(4) *Without vitamin B_{12}, the bone marrow produces few red cells and most of them are abnormal: either small and of irregular shape, or mainly giant cells (macrocytes). The average volume of the corpuscles in pernicious anaemia is considerably increased, and the amount of haemoglobin in each is correspondingly greater than normal (hyperchromia).*

(5) *Not all parasitized persons suffer from this disease; it appears that some are predisposed to it by an inherited factor.*

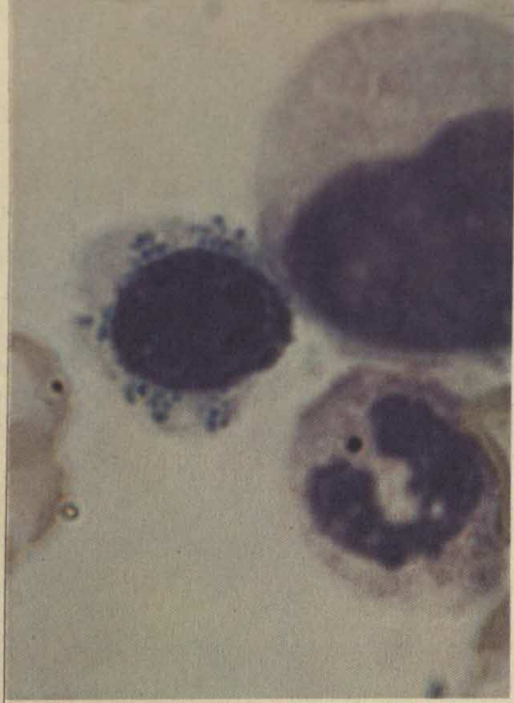
(6) *The layer of fatty tissue immediately underneath the skin, or superficial fascia.*

(7) Normal blood iron: *110–120 γ in men, 90–100 γ in women.*

(8) Eosinophil: *a type of leucocyte characterized by a big multi-lobed nucleus and large granules which are easily stained with eosin. These cells make up 1 per cent to 3 per cent of the polymorphonuclear cells of an adult in normal health; their number may be increased three or four times in certain diseases. Eosinophilia is particularly frequent in parasitic infections.*

(9) Haemolytic anaemia *is the result of an abnormal destruction of red cells, usually owing to an inborn defect in the cells and in their haemoglobin, but it can also be produced by chemical poisons or bacterial toxins.*

(10) *See the chapter on 'Heredity' by Maurice Lamy, p. 138.*



Iron-containing erythroblast in a case of sideroblastic anaemia. Chromatin is particularly well seen in the polymorphonuclear cell at bottom right. (Photo Lod).

miasis is common among miners, farmers, and others who are much in contact with the soil. It is caused by *Ankylostoma duodenale*, a nematode worm, rosy-white in colour, bent like a comma, and varying in length from one to two centimetres. The larva of this worm is extremely small, not more than half a millimetre long, and lives in the ground. Given the opportunity, it enters the human body by piercing the skin, then travels via the lymphatic system to the lungs, whence it is coughed up and swallowed, thus reaching the digestive system. Here it develops, and the adult worm attaches itself to the duodenal mucous membrane by means of four tiny chitinous teeth. This causes a slight but continuous loss of blood, and, in predisposed persons, the appearance of anaemia.

This type of anaemia is never extreme: the number of red blood cells does not fall below one and a half million per cubic millimetre, or the haemoglobin below 25 per cent of normal. The red cells are usually smaller and contain less haemoglobin than normal. *Eosinophilia*,[8] which is pronounced, is very helpful in the diagnosis of these cases. The disease runs a chronic course, but can be quickly cured by eliminating the parasite from the intestine with a suitable vermifuge and at the same time administering iron.

The nutritional hypochromic anaemia of childhood is the commonest type of anaemia between one and two and a half years of age. It usually occurs in infants that are fed for too long on milk alone, whether maternal, cow's or goat's. It usually affects children of the poorest classes, for whom milk—particularly the mother's—is the cheapest and easiest type of baby food.

Milk contains very little iron, so that when an infant's reserves of iron (accumulated during foetal life) are exhausted, the lack of it is felt. There is serious interference with the production of haemoglobin, and anaemia is the obvious result.

This type of anaemia usually disappears spontaneously at the time of weaning, when the baby begins to take a variety of foods as well as milk, of which some (eg, meat, and certain vegetables) contain plenty of iron. Oral administration of iron is the best treatment for this type of anaemia.

Haemolytic anaemia

Congenital haemolytic jaundice,[9] an hereditary disease transmitted by a dominant[10] factor, is more common among white than among coloured people. Its cause is an inborn defect in the maturation of the red blood cells; most of them are produced by the bone marrow in smaller and more spherical form than the normal biconcave discs. They are also more fragile than normal cells. The result of this abnormal form is that the 'life' of the red cells is considerably shortened: instead of the usual 120 days,[11] they survive for two weeks at most. It is the specific function of the spleen to collect abnormal cells from the circulation and destroy them by phagocytosis.

Although this type of anaemia is congenital, its symptoms, jaundice and enlargement of the spleen, often do not appear until adult life.

Jaundice is what the patient notices most; its development is slow and characterized by attacks of variable frequency, alternating with periods when it partly or entirely recedes. During an attack, the skin is distinctly yellow and the urine dark. When it recedes, the jaundice fades and can often be detected only in the whites of the eyes (subicterus). This slight degree of jaundice is often present from early childhood.

The anaemia also undergoes successive exacerbations, but begins insidiously and its development is so slow that it may be quite severe before the sufferer is aware of it. Enlargement of the spleen is almost invariable and causes a feeling of fullness in the left side; the liver is also slightly enlarged. Thus the jaundice and the anaemia progress together, attacks of one leading to aggravation of the other.[12]

This type of haemolytic anaemia follows a typically chronic course; the patients usually keep fairly well in spite of it. The only treatment is palliative, the operation of splenectomy.

Thalassaemia, or *Mediterranean anaemia*, is the name given to a group of hereditary anaemias, characterized by the formation of a defective type of haemoglobin: haemoglobin A is produced in a reduced amount,[13] and the production of haemoglobin F persists as the result of a compensatory mechanism.[14] The red cells are small (microcytes) and usually pleomorphic and their average length of life is always shorter than normal.

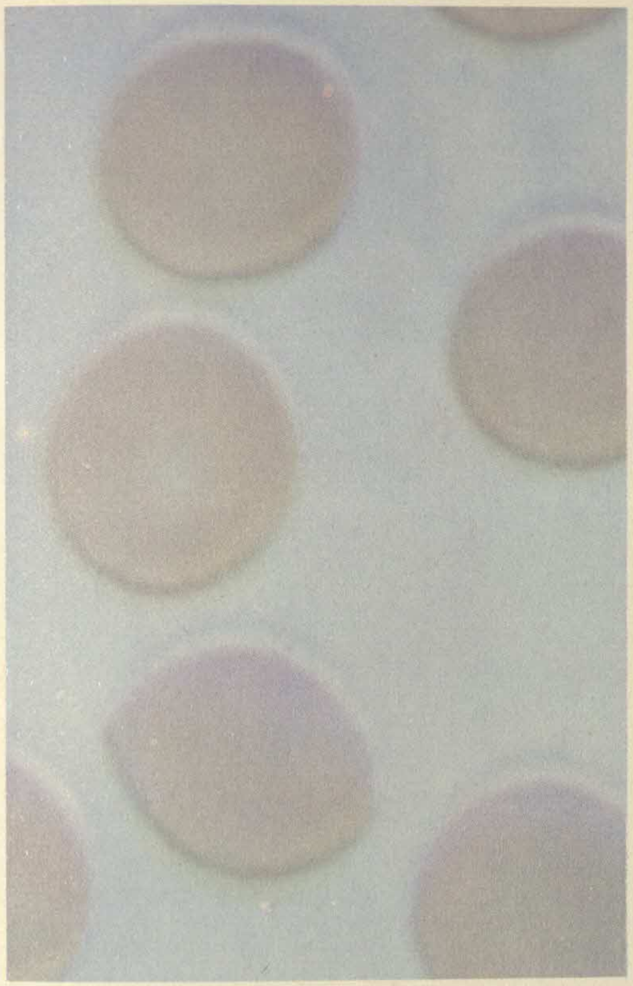
Mediterranean anaemia is common not only among those living near the shores of that sea, but also among Africans and Asiatics, particularly Chinese. Three main forms of it are distinguishable clinically. The most serious type is known as thalassaemia *major* or Cooley's anaemia. It occurs in young children and is invariably fatal. The milder form, which is

(11) *The length of life of red cells has been determined with great accuracy by marking their haemoglobin with radioactive iron* (^{59}*Fe*).

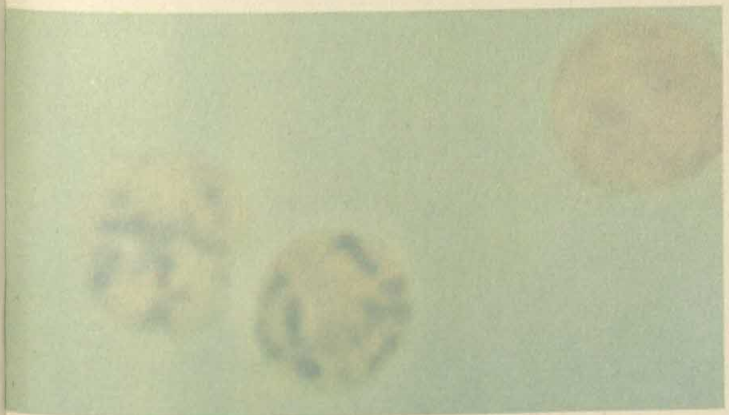
(12) *The haemoglobin resulting from the destruction of red cells is normally converted into a golden-yellow pigment called bilirubin which is excreted by the liver in bile. If, through the destruction of red cells the formation of bilirubin increases, or if for any reason the liver is unable to excrete the pigment, bilirubin accumulates in the blood and permeates the whole organism, giving it a characteristic yellow colour* (jaundice).

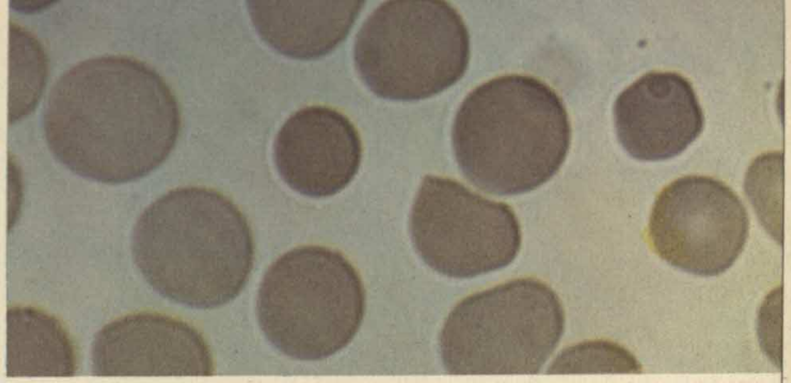
(13) Haemoglobin A *is the type of haemoglobin found in the red blood cells of normal adults.*

(14) Haemoglobin F *is the foetal haemoglobin normally present in the red cells during intra-uterine life and the first few months after birth. This haemoglobin has the property of being resistant to alkaline denaturation, whereas other haemoglobins are alkali-sensitive.*

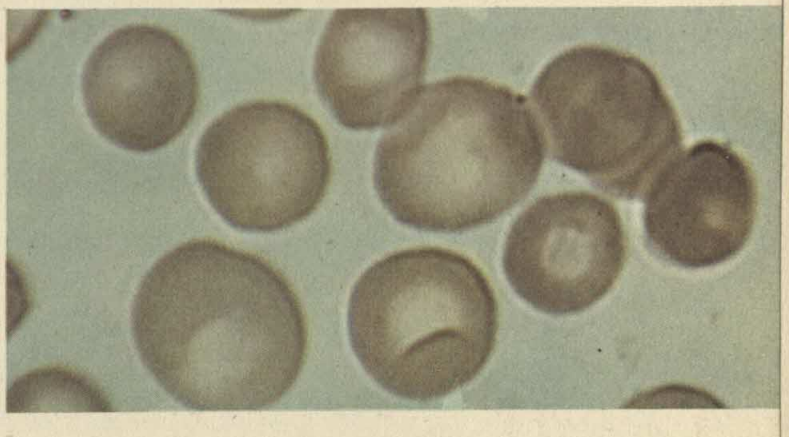


Above, red cells (mag. × 5,000); below, reticulocytes of normal blood (mag. × 2,400); compare their regular shape with the abnormal forms in the other illustrations. (All photographs on this and the opposite page were taken at the Blood Transfusion Centre of the Department of the Seine, Director, Dr R. André, with the collaboration of Dr Combrisson. Photos Lod).

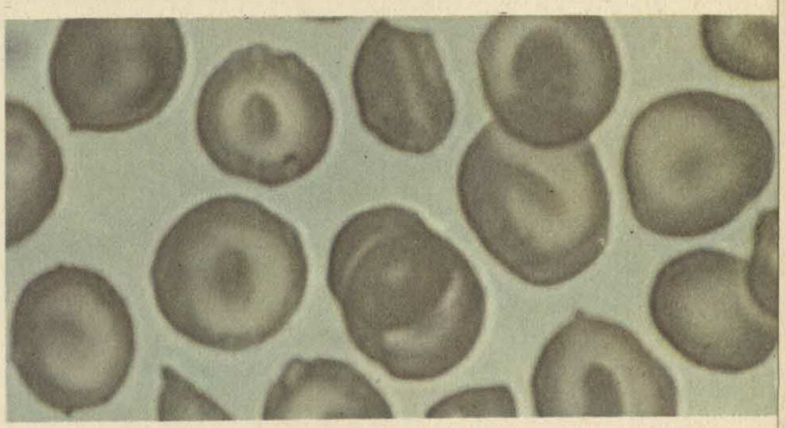




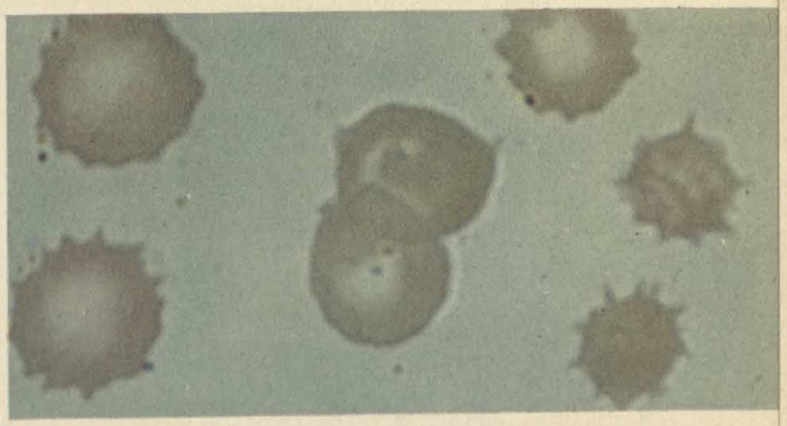
The presence of many spherocytes (there is a typical one in the centre) among the red cells indicates a spherocytic type of haemolytic anaemia. (Mag. × 2,200).



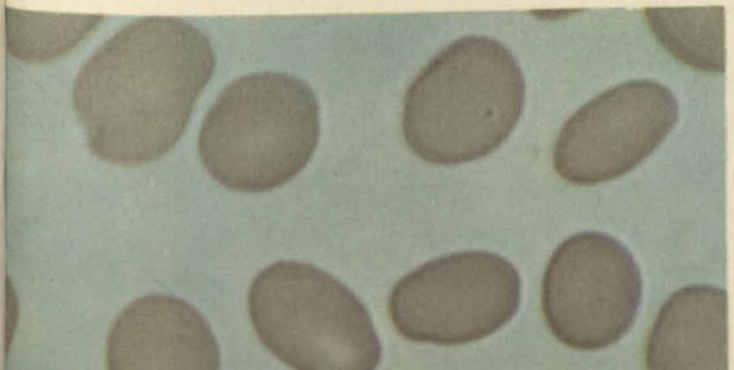
The red cells are larger than normal: from a case of megalocytic or pernicious (Addison's) anaemia. (Mag. × 2,400).



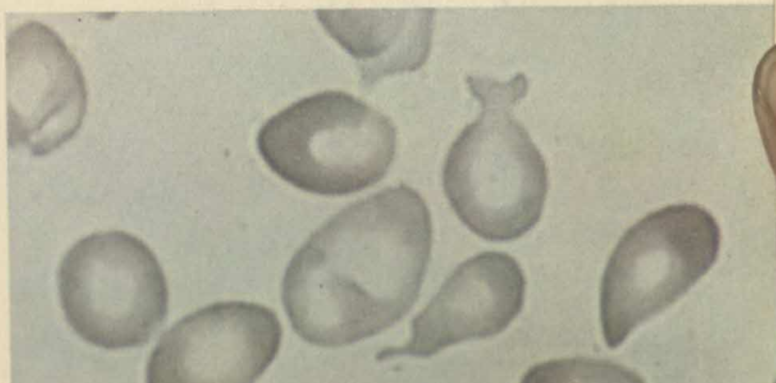
Thalassaemia, a congenital abnormality of haemoglobin, is characterized by the presence of 'cockade' or 'target' cells. (Mag. × 2,400).



Acanthocytosis: an hereditary disorder affecting lipid metabolism. The cell-membrane is deformed into a 'sea-urchin' or 'prickle-leaf' pattern. (Mag. × 2,400).



Ovalocytes: a congenital haemolytic anaemia due to cells of this abnormal shape. (Mag. × 2,200).



These cells in the shape of a 'bicycle wheel' look deformed and hollow because all their haemoglobin is at the periphery. This occurs in the hypochromic anaemia which follows severe haemorrhage. (Mag. × 2,400).

compatible with growth to adult life, is called thalassaemia *minor*, or Rietti-Greppi-Micheli syndrome. Finally, there is thalassaemia *minima*, which is hardly a disease. Persons affected by it feel perfectly well, but examination of their blood shows to an inconspicuous extent the changes characteristic of the two other forms of thalassaemia.

Sickle-cell anaemia is another hereditary haemolytic anaemia, which originates from the synthesis of abnormal haemoglobin. The sickle-shaped cells contain the pathological form of haemoglobin S[15] instead of the normal haemoglobin A. Sickle-cell anaemia has so far been observed only in Negroes, Arabs, and in half-breed populations.[16] As in thalassaemia, there are individuals in whom the disease is manifest (homozygotes), who are doomed to an early death, and those who are apparently healthy (heterozygotes), but who yet have the sickle-cell trait in their blood.

Favism is an hereditary disease common in Italy (especially in Sardinia). It is characterized by haemolytic crises, sometimes severe, which occur, especially in young people, several hours after eating a particular type of bean. This disease is due to an hereditary enzyme defect of the red blood cells: the absence of the enzyme glucose-6-phosphodehydrogenase.[17]

Haemolytic disease of the new-born, or *erythroblastosis foetalis*, is characterized by the presence of erythroblasts[18] in the blood. It is rarely seen in the first child of a family, but more often in the second or in later children.

Erythroblastosis only attacks the foetus or new-born baby when the father has a different blood-group from that of the mother: usually the infant is Rhesus-positive and the mother Rhesus-negative. In about 10 per cent of cases the disease is due to the baby having blood-groups A, B, or AB and the mother group O. Although this difference in blood groups is an essential of the disease, it is not in itself sufficient to cause the disease to develop; this happens only when the placenta is damaged so that a few of the foetal red cells pass through it and enter the mother's circulation. As a defence against the 'foreign' cells, which are of a different group, the mother's immunity mechanism produces antibodies capable of destroying these cells; but as well as doing this in the maternal circulation, these antibodies pass across the placenta into the baby's blood, where they continue to act. As a result, the foetus develops anaemia and jaundice.

In the most severe cases of erythroblastosis the foetus dies and is prematurely stillborn. If, however, the pregnancy continues to term, there may be one of three results: *hydrops foetalis*, which is always fatal, *icterus gravis neonatorum*, or simply haemolytic anaemia.

Icterus gravis is marked by anaemia and a yellowing of the skin, which deepens hourly; nervous symptoms are also very common (drowsiness, twitching and coma). Several years ago, the mortality rate was 80 per cent, and in 10 per cent of the survivors there was severe spastic[19] paralysis. Now, exchange blood transfusion, [20]which must be performed during the first nine hours after birth, has reduced the mortality to 10 to 20 per cent.

Fortunately, however, the commonest form of erythroblastosis, known as 'haemolytic anaemia of the new-born', is also the least severe. It may be apparent on the third or fourth day of life and develop slowly over a period of one or two months. Treatment of the most severe cases is by exchange transfusion, but a simple blood transfusion is usually sufficient for milder cases. No treatment at all is necessary for less severe cases.

Thus we see the complexity of the actiological diagnosis of the anaemias, and the necessity for careful investigation before starting treatment.

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[15] Haemoglobin S *differs from normal haemoglobin in its electrophoretic behaviour. There are other abnormal haemoglobins, which may occur singly or in combination, as inherited disorders: namely, C, D, E, G, H, I, J, and K. The order of their electrophoretic mobility is as follows:*

SG
CE AJIHK
DF

Because of its frequency and severity, sickle-cell anaemia is by far the most important disorder of haemoglobin.

[16] *The relative frequency of these affected individuals, and to some extent their geographical distribution, are due to a remarkable fact: affected heterozygotes are more resistant to malaria than are normal persons, so that over the centuries they have enjoyed an advantage in selection for survival.*

[17] *The same enzyme defect has been observed in persons who are hypersensitive to particular substances (eg, anti-malarial drugs, antipyretics, sulphonamides, etc). Ingestion of the substance to which they are sensitive may cause such persons to have a haemolytic crisis.*

[18] Erythroblasts: *immature red cells normally present in the bone marrow, but not in the blood.*

[19] Spastic: *characterized by the occurrence of muscle contractions.*

[20] Exchange transfusion *consists of an injection of 500 cc of blood, with simultaneous withdrawal of 440 cc; in this way 'healthy' blood is substituted for the new-born baby's own blood, in which antibodies produced by the mother would have continued to destroy the infant's red cells.*

Atherosclerosis and myocardial infarction

Jean LENÈGRE

Infiltration of the arterial walls by lipids, which leads to atheroma and arteriosclerosis, begins early in the human species and is present in some degree from adolescence onwards. When the coronary arteries of the heart are involved, it may lead to a blockage which causes infarction of the cardiac muscle. As a result of medical progress, the outlook for this condition has improved and recovery is now usual.

Atherosclerosis affects especially the innermost wall (*intima* or endothelium) of large and medium-sized arteries, and is produced by a combination of two basic pathological lesions: (a) the atheromatous plaque consisting of lipid deposits, and (b) fibrous thickening.

When atherosclerosis is extensive, thickening of an artery's walls at the expense of its lumen[1] reduces the calibre, or even causes complete obstruction, so that the region supplied by the artery becomes deprived of blood. Some degree of atherosclerosis is found in all human beings once they reach a certain age—about thirty to thirty-five in men and forty to forty-five in women. In most people, although it may be fairly generalized, it fortunately does not reach the point where it jeopardizes the circulation to vital organs. For this reason, atherosclerosis is in most of us a silent and symptomless process.

In a minority, however, variously estimated as from 15 to 50 per cent of the population over fifty years of age, the condition is of serious significance, either because it extends throughout the arterial system, or because it attacks one or more of the vital organs.

The factors that lead to a severe degree of atherosclerosis in certain individuals are many and varied: in some there are haemodynamic factors, such as arterial hypertension; in others, endocrine disorders, such as an early menopause (natural or induced), or thyroid insufficiency, or metabolic disturbances, such as diabetes mellitus and other causes of sustained hypercholesterolaemia; and in others, hereditary or genetic factors, for it appears that certain families are more susceptible than others to the effects of atherosclerosis.

Whatever the cause, when atherosclerotic lesions have progressed to such an extent as to cause a significant reduction in the lumen of an artery supplying some vital tissue, there may be serious consequences. Among these, in decreasing order of importance are: heart attacks, cerebral vascular accidents, renal insufficiency, and ischaemia[2] of arteries to internal organs or limbs. All result from a reduction in the blood supply of the tissues supplied by the narrowed or blocked artery, causing deficient oxygenation or anoxia. According to its degree, this anoxia of the tissues may cause either some temporary disturbance until it can be relieved by the development of a collateral circulation, or permanent damage due to death of the tissues whose blood supply has failed.

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(1) Lumen: *effective diameter of the artery.*

(2) Ischaemia: ***localized anaemia, or interference with the blood supply to a part of the body. Here it is due to almost complete obstruction of an artery.***

Myocardial infarction

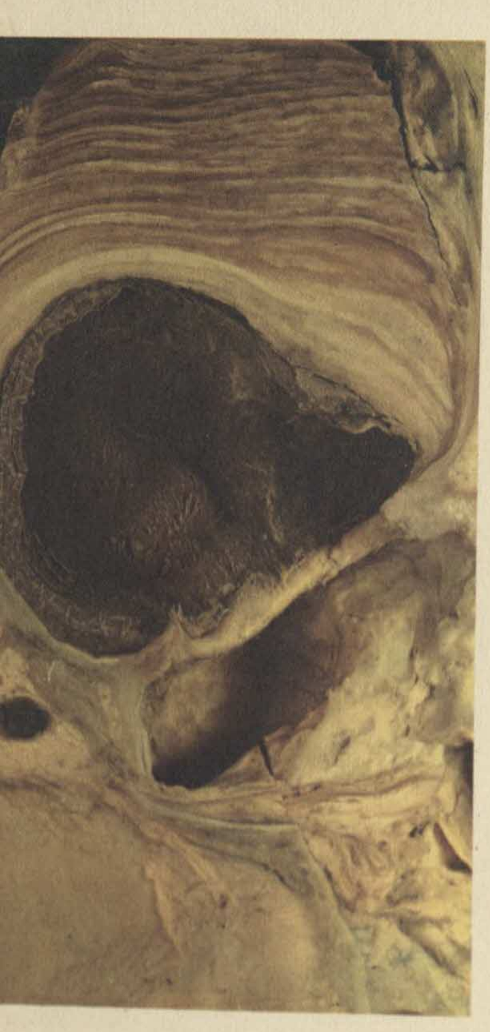


Fig. 1. This photograph shows a typical aneurism of the aorta, with a localized dilatation. (Photo Lod, taken in the museum of Professor Kourilsky's medical unit, Hôpital St Antoine, Paris).

A myocardial infarct is an area of damage, localized but serious, in the heart wall, resulting from an interruption or reduction in blood flow through the coronary artery which supplies it.

Less than fifty years ago, myocardial infarction was rarely diagnosed, even by cardiologists. Since the development of electrocardiography, however, doctors have learnt much about the diagnosis of myocardial infarction, which now appears to be one of the commonest types of heart disease. In 90 per cent of cases it is associated with coronary atherosclerosis, or with a lesion that frequently accompanies it—fibrinocellular thrombosis³ of a diseased coronary artery, to which men of fifty to sixty are particularly subject. Women are affected less often and at a later age; different authorities estimate the incidence in men as being two to five times higher than in women. The disease is not limited entirely to those of middle or later age; it may be seen in persons less than thirty-five years old and even in children, though this is extremely rare.

The mechanism by which coronary atherosclerosis leads to myocardial infarction is simple in one way and complicated in others. It is simple in the sense that myocardial infarction is always due to a significant reduction in the flow of blood, ie, below the minimum required to sustain its life, to a given part of the heart; it is complicated in that many factors may be involved in determining this reduction in a sclerotic coronary artery. There are, for example, mechanical factors, such as the narrowing, progressive occlusion, or sudden thrombosis of the artery; or accidental factors like arterial spasm or pressure variation in the coronary circulation: a reduction in blood pressure leads inevitably to a diminution in blood flow. In other cases, there is a sudden increase in the demands of the myocardium for blood, ie, for oxygen; a violent physical effort or strong emotion, such as rage, increases the work of the heart and consequently its need for oxygen, and if the coronary arteries are already diseased, rigid, sclerotic, and therefore incapable of dilating, this need may not be fulfilled.

In nearly half the cases, a myocardial infarct does not appear 'out of the blue'. It is preceded in 40 per cent of them by warning signs which, if understood and heeded, would in many cases prevent serious trouble. These warnings consist mainly of pains in the chest or arms which come on suddenly, sometimes spontaneously but more often during exertion, typically in a man of about fifty who has hitherto been strong and active. As has often been said, it is a 'disease of executives'.

When the pain occurs during exertion, a person usually stops what he is doing and the pain ceases as if by magic. Because of this, those who suffer from it usually dismiss it from their minds, thinking it to be due to indigestion or to swallowing some air. It is a curious fact that those who have organic heart disease consult cardiologists only occasionally and reluctantly, but many persons who are afraid there is something wrong with their hearts and that they are going to die, and who are generally called neurotic or hypochondriac, worry about vague or non-existent aches and pester their doctors unnecessarily.

The chest pains which precede a myocardial infarct are only temporary: either they fade away and disappear without leaving any trace (though, of course, there is always a danger of their returning) or they become more frequent and more severe until at last the myocardial infarct occurs. This has long been attributed to coronary thrombosis, ie, the obstruction of a coronary artery by a blood-clot which forms in it, which is certainly the usual, though not invariable, cause of a myocardial infarction, but it is possible for one to occur without coronary thrombosis, and *vice versa*.

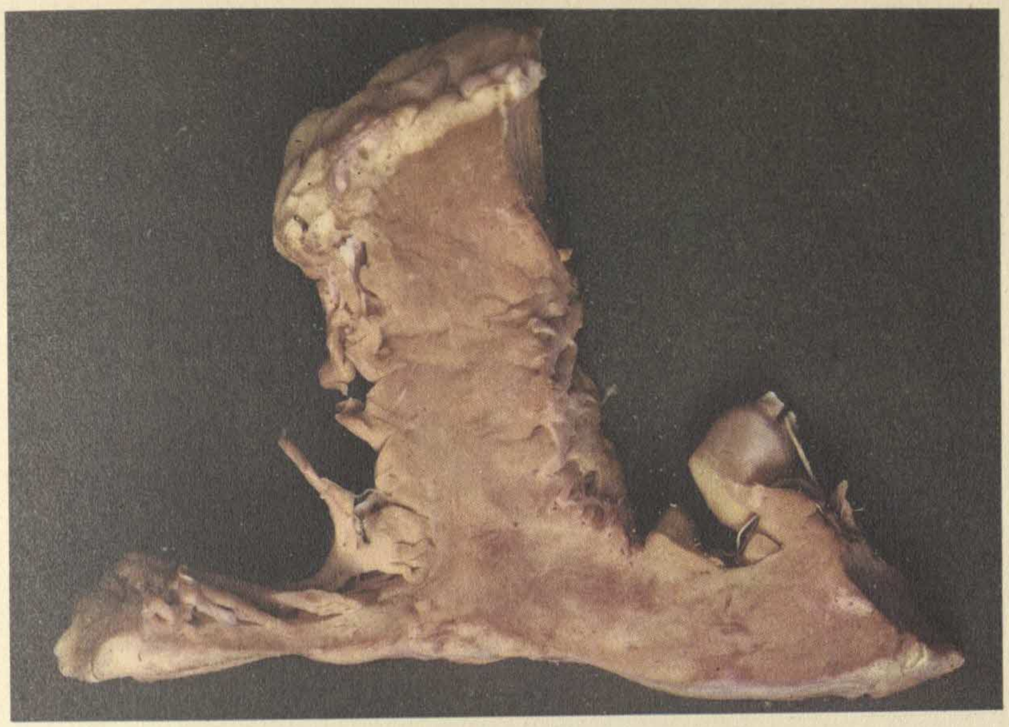
A myocardial infarct does not always present the characteristic clinical picture; it may be accompanied by a severe chest pain at the beginning, but it can also be deceptively stealthy, giving the impression, for example, of an attack of indigestion, perhaps with nausea or vomiting. This is why such an infarct sometimes goes unrecognized and is only discovered by chance, perhaps when an electrocardiogram is taken for the purpose of life insurance.

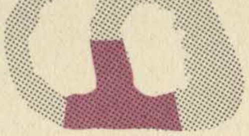
Whether its onset is marked by severe or mild symptoms, myocardial infarction is always a serious illness: its occurrence may be suspected clinically, with a history of suggestive symptoms, by taking the patient's temperature (which rises to 38° or 39°C the day after the attack of pain) and blood pressure, which tends to fall during the next few days. However, the diagnosis can only be confirmed by blood tests, and more especially by electrocardiography.

Diagnosis and treatment

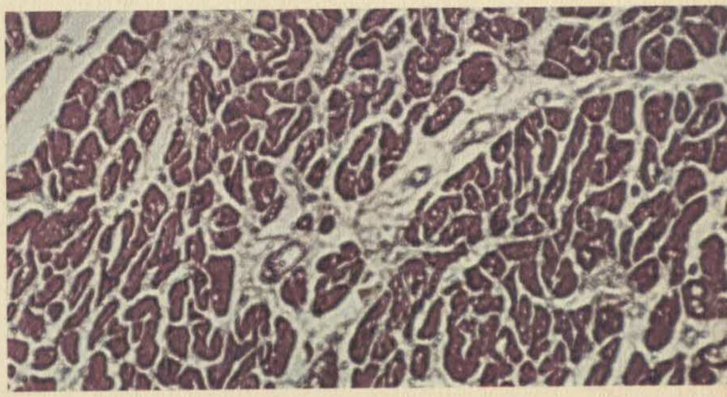
Among the many possible blood tests, one is of particular value: the determination of the

(3) Thrombosis: *formation of a clot in a blood vessel or chamber of the heart during life.* Fibrinocellular thrombus: *a clot formed from fibrin, in whose whitish elastic strands are entangled the formed elements of blood, ie, red and white cells.*

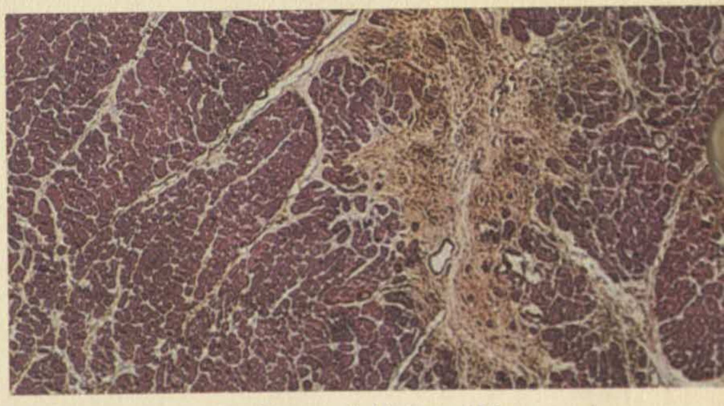




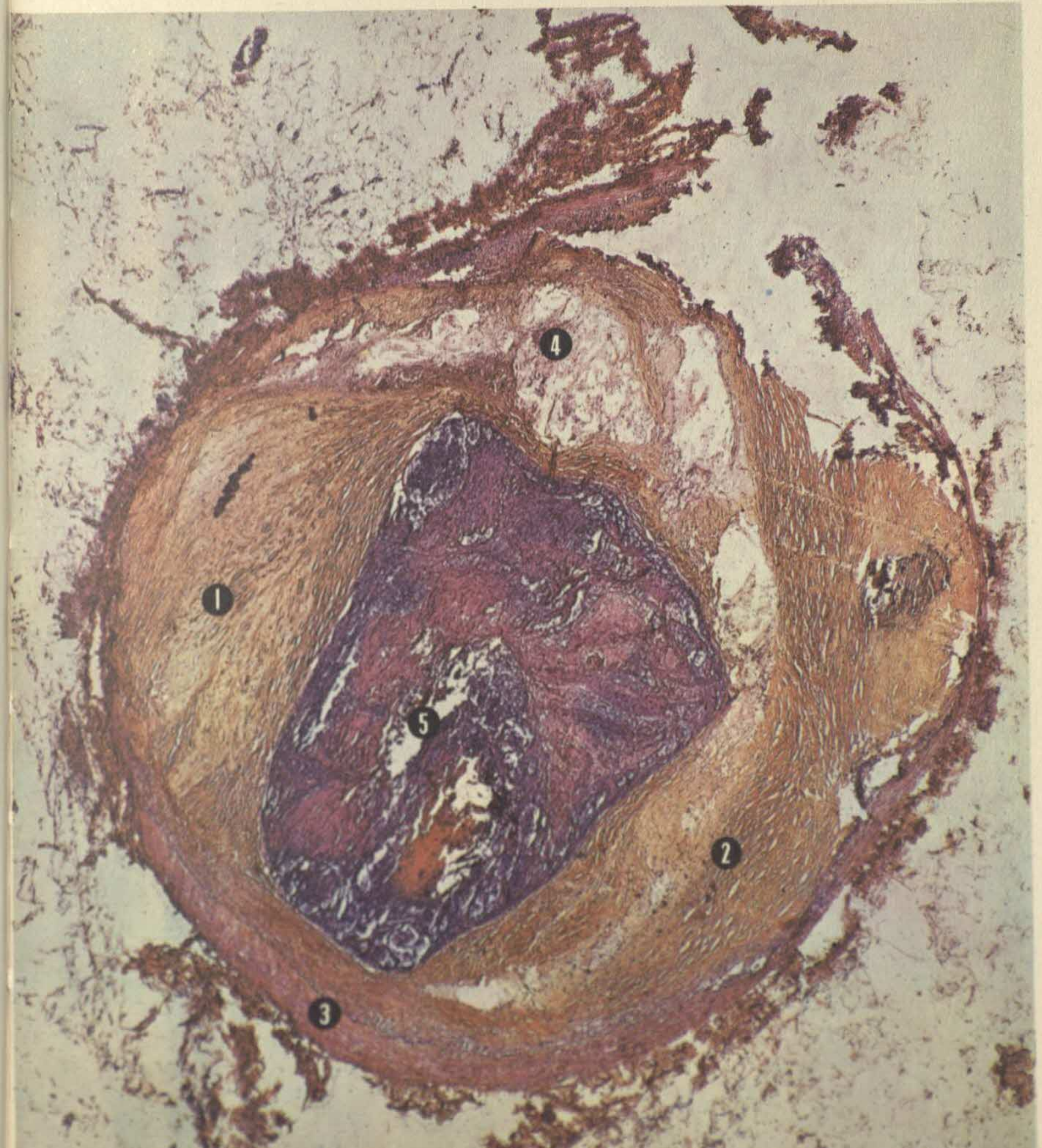
The photograph opposite shows a transverse section of part of the interventricular septum and of the anterior walls of the right and left ventricles (the diagram shows the relationship of this section, coloured red, with the rest of the heart). The lesion, or infarct, is the slightly blurred multi-coloured area, which extends from the septum to the anterior wall of the left ventricle. (Preformation by Serrurier; photo Lod).



Histological structure of a normal myocardium. (Mag. × 150).



Fibrous scar of a localized myocardial infarct. (Mag. ×42).



Section of a coronary artery narrowed by the deposition of lipid masses, which are clearly seen in its wall. The lumen of this artery is completely obstructed by a blood clot (thrombus). 1 and 3, wall of the artery; 2 and 4, cholesterol; 5 clot. (Mag. ×26. Photo Lod).

level of the enzyme glutamic oxaloacetic transeminase is raised in nearly all cases of myocardial infarction to well above the upper limit of normal (40 units), sometimes to a level of 100 units or more, reaching its maximum twenty-four to forty-eight hours after the attack. This method of estimation is of practical use in diagnosis because it is a measure of specific damage to the heart-muscle fibres; but its value is limited by the fact that the transaminase returns to normal by the fourth or fifth day, so that the test is only useful for the first three to four days; after this, the blood sedimentation rate is of more value, for in more than 80 per cent of cases it is considerably raised: this effect may last for several weeks, but it is not specific for myocardial infarction and the rate may be raised in many other conditions. Indeed, the electrocardiogram is still the most important single test in the diagnosis and treatment of this condition. Abnormalities are often observed in the first few hours, and if not immediately decisive, the electrocardiogram becomes so within twenty-four to forty-eight hours of a myocardial infarction. Furthermore, it gives valuable indications of the site, extent and seriousness of the lesion.

Myocardial infarcts may be divided into three categories: anterior, posterior, and lateral, each of which gives a characteristic electrocardiographic pattern.

In the light of his clinical examination of the patient, and aided by the results of special investigations, the doctor can decide upon appropriate treatment, of which prolonged rest in bed is the most important. Usually, a myocardial infarct causes a definite illness, with general malaise and fever for about a week. But it would be unwise to think that because the outward and visible signs of the disease subside after a few days, the illness is over. The structural alterations that have taken place in the heart muscle take much longer to heal, for they must undergo a cycle of changes finally resulting in the formation of a fibrous scar. Serial electrocardiograms enable this process to be watched and followed.

Scar formation will usually have progressed sufficiently for the patient to get up after three to five weeks, and to allow the resumption of normal activities after two to three months; it reaches its final state in four or five months. These estimates have been confirmed by experiments on animals and must always be borne in mind when a patient is being treated for myocardial infarction, however well he may appear to be. Anyone who has recently suffered an attack should be in bed and completely at rest for three to four weeks; he can start getting up in his room towards the end of the first month, and going out after six to seven weeks. Then, after a full month's convalescence, ie, two to three months from the beginning of his illness, he may gradually return to his normal occupation.

In more than half the cases that occur, a myocardial infarct heals without leaving any sign, except for some residual abnormalities in the electrocardiogram; in fact, the patient is cured. But he must remember that he has had a stern warning.[4]

In a small number of cases, a myocardial infarct is followed by symptoms which vary from slight pain in the shoulder to cardiac failure.

It is possible for myocardial infarction to be fatal, especially in the first few days. But this result, which used to be fairly common and has given the disease such a sinister reputation, now appears to be relatively rare: perhaps because myocardial infarcts are better diagnosed than they used to be, and the less severe and less extensive ones are recognized; perhaps also because there have been important advances in treatment. Myocardial infarction nowadays carries a prognosis which is nearly always favourable; provided they undergo proper treatment and live regular lives thereafter, sufferers from the disease can look forward to a return to health and a good expectation of life.

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(4) *If the patient is to return to the normal round of social, professional and family life, he must observe certain rules, such as the avoidance of too much rich or fatty food and tobacco.*

High arterial pressure

W. S. PEART

To understand high blood pressure it is necessary to consider the basis of the circulation. As was shown by Harvey, the heart pumps the blood into the arteries, which break up into small hair-like muscular arterioles which provide the resistance. With each heart-beat the arterial pressure rises and then falls as blood flows through the resistance of the arterioles into the veins.

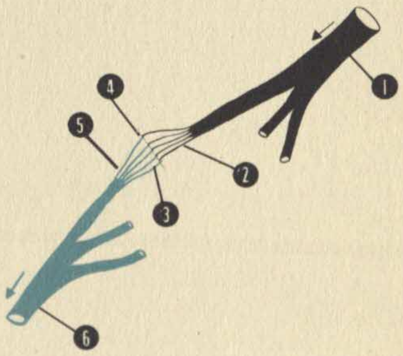


Fig. 1. Diagram of circulation; arterial blood is turned into venous blood in the capillaries. 1, artery; 2, arteriole; 3, capillary; 4, site of metabolic exchanges in the tissues; 5, venule; 6, vein.

It is understandable that the arterial pressure will rise if either the output of blood from the heart or the resistance of the arterioles increases. In practice, if either of these things happens, compensatory changes occur which tend to return the blood pressure to normal. The arterial pressure in man is normally set at about the figure of 120 mm Hg systolic and 80 mm Hg diastolic. This is not the pressure for all animals, but is the usual figure in man. The most important function of the circulation is to supply blood in adequate amounts to vital organs, and the blood pressure will be at a level which is governed by the relation between the resistance to flow in various parts of the body (total peripheral resistance) and the output of the heart. However, certain organs are of greater importance than others and much more sensitive to lack of blood. The skin can be deprived of blood for hours and yet survive on return of the circulation. The brain dies after deprivation for only a few minutes. It is not surprising, therefore, that control of the blood pressure, and thus of blood supply, rests largely in the brain. If the blood pressure is suddenly lowered, nervous reflexes come into play to return the blood pressure to normal. This leads to intense vasoconstriction in the skin and other areas, so that blood is diverted to the vital parts of the brain. Its most sensitive vasomotor areas are found in the hypothalamus and the medulla.

In addition, there are other areas in the circulation itself which act as sensing devices, baroreceptors, and which have a reflex influence on the blood pressure by affecting the tone of the arterial wall and thus the peripheral resistance. One of the most interesting of these areas lies in the wall of the internal carotid artery at its origin. This artery carries a major supply of blood to the brain.

The work of Hering, and of Heymans and his school, has shown that raising the pressure

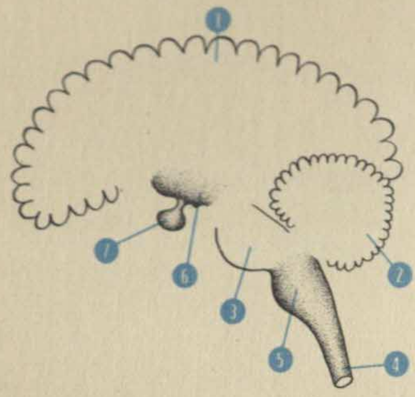


Fig. 2. Centres controlling circulation. The most sensitive vasomotor centres are in the medulla (5) and in the hypothalamus (6). 1, cerebral hemisphere; 2, cerebellum; 3, pons varolii; 4, spinal cord; 7, pituitary.

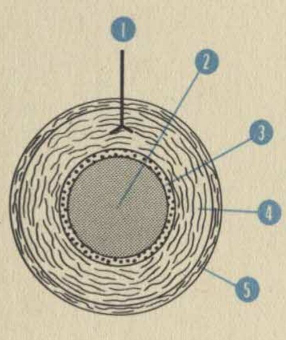


Fig. 3. Section of arteriole showing the three tunicae of the arterial wall. 1, sympathetic nerve fibre; 2, channel of arteriole; 3, tunica interna; 4, muscular tunica media; 5, tunica externa.

in this region of the artery will, by reflex action, lower the blood pressure, and conversely, lowering the pressure of the carotid sinus will raise the general pressure. This is achieved by stimulating the sensitive nerve endings which terminate in the wall of the carotid sinus and which, when it is stretched, as by changes in pressure in the carotid sinus, send impulses to the brain. It is understandable that this sensitive area should be on the artery to the brain, and while there are other baroreceptor sites in the vascular system, this is the one that has been most fully investigated. While it is easy to see that in the course of evolution reflexes may be acquired which restore the blood pressure to normal by increasing peripheral vasoconstriction or the cardiac output when the blood supply to the brain is reduced, it is not so easy to see why it should be necessary to reduce a high blood pressure, since in the tissues this would only lead to increased flow, which would not presumably have any serious consequences. In any event, a high blood pressure is not a very strong stimulus to the carotid sinus, except for a very short time. It seems that the nerve endings in the wall respond only to a rapid rate of change, and then settle down, as if accustomed to the higher pressure. This has been shown by the admirable experiments of McCubbin, Green and Page. If these depressor reflexes were effective, this chapter would not need to be written, because high arterial pressure would never occur.

Measuring of high arterial pressure

There has been a great deal of discussion about the definition of high blood pressure and when it may be considered to exist. This introduces the variable factor of age. Does blood pressure naturally rise with age, or does rising blood pressure represent a disease or change in blood vessels that is not necessarily a part of growing old? There has been controversy about this and about the related topic of the inheritance of high blood pressure. Pickering and his colleagues have put forward the view that the level of arterial pressure is inherited, and that in the relatives of someone with high arterial pressure this pressure will be higher than in the relatives of someone with a normal pressure. Furthermore, this relationship is so at all ages, and the mean arterial pressures of persons with or without high blood pressure, as well as that of their relatives, rises with age. This view has been strongly challenged by Platt and by Morris, who believe that there is a group of persons with a more dominant type of inheritance. It is well known that in some cases blood pressure has stayed at 120/80 or at 160/100 for twenty years, and it seems that the truth lies somewhere between these extreme views. The emphasis on environmental factors, brought out by recent population studies, seems to be a particularly important point. In many biological problems it is sometimes forgotten that the environment, as well as the genetic constitution, is often 'inherited'. All these studies have been made on populations in which no obvious cause of high arterial pressure has been found. In those in whom it occurs it is therefore defined as 'essential' or 'idiopathic', constituting what I regard as a rather unrewarding group for study under this heading.

The approach to this problem reflects two interesting philosophies of research work. If it is believed that the population under study is homogenous (and by definition it must be) and the hypertension is therefore called idiopathic, then much research effort will be expended on the type of study that seeks for environmental and inherited factors. On the other hand, the view that individual causes should be looked for leads to a very intensive search in small numbers of patients for diseases known to cause high blood pressure. It will be interesting to see which approach is finally the most fruitful. Hitherto, the latter has been that generally adopted in medical research.

As I believe this method to be less prone to fallacy, it is natural that this discussion of high arterial pressure should now be turned to the known causes. Initially, it was stated that a rise of cardiac output would raise the arterial pressure if the arterial resistance was unaltered. Usually, most conditions associated with raised cardiac output (eg, fever, overactivity of the thyroid, severe anaemia) are not characterized by markedly raised arterial pressure. They may be neglected as a factor in most forms of human disease, while concentration is directed towards raised peripheral resistance. It can be shown that in most forms of human hypertension there is greater constriction of the arteries than is normal. This was first clearly established by Pickering in a study of the circulation of the hand. The blood flow in a group of patients with various causes for their hypertension was found to be completely normal. As the arterial pressure was much higher than normal, this must mean

(1) Collagen: *the protein of the fibrous connective tissues made by cells called fibroblasts.*

that the resistance to flow is much greater in hypertensive individuals.

Causes of resistance

We can now, therefore, consider the influences which may play a part in governing the resistance of the arteries.

1. *Blood viscosity*

It would be natural to suppose that conditions which raise the blood viscosity would increase the resistance, and therefore the arterial pressure. However, where the viscosity is considerably raised, as, for example, by increasing the proportion of red cells to plasma (polycythaemia), hypertension is not a notable feature. For example, a patient whom we once examined had a proportion of red cells to plasma of 76-24, compared with the normal 45-55; this was associated with a considerable increase in viscosity as measured *in vitro*, yet hypertension was absent.

2. *Thickness of the intima*

This structure is composed of a thin layer of cells resting on a layer of elastic and fibrous tissue. Obviously, if the latter were thickened through some cause or other, increased resistance to flow would result. It is known that one of the consequences of human ageing is that disease of the intima occurs, leading to the deposition of cholesterol as yellow plaques. This mainly affects the larger arteries, though the smaller arteries and arterioles are not immune. In the arterioles, a fibrous thickening occurs, which is usually a consequence of high blood pressure rather than its cause. The suggestion has been made that an actual swelling of the wall, caused by imbibition of water and electrolytes under the influence of substances resulting in a raised arterial pressure, could actually be responsible for the increased resistance. The collagenous[1] protein of the subintimal tissues is known to have a high affinity for water and electrolyte, but there is no direct support for this attractive idea. Apart from reduction of the lumen, length and sinuosity ought to be briefly considered. It is a common observation that in high arterial pressure the arteries and arterioles are sinuous and elongated (fig. 1). This increase in length could be a factor in increased resistance, but it is perhaps more usually a consequence of the high blood pressure.

3. *Contraction of muscle*

The muscle in the arterial wall is of the variety known as smooth, and is not under voluntary control. It has intrinsic tone, by which is meant that it responds to stretching by a maintained tonic contraction. Folkow has shown that in the cat increase in the pressure in the arteriole leads to an extra contraction in the muscle. This would, of course, increase the resistance further and raise the arterial pressure. If this response to a rise in pressure were exaggerated, then it might be a cause of persistent arterial hypertension. There is no evidence of this, however. More needs to be known of the basic physiological responses of the smooth muscle, and in particular of its metabolic processes, since cells which can maintain their protein, 'myosin', in a state of contraction indefinitely, are of great interest. Factors which could influence these metabolic processes could obviously play a part in controlling the arterial resistance. Friedman and Friedman have shown that some natural substances which raise the arterial pressure by directly constricting the arterioles cause large shifts of sodium and water into the arterial wall, and it is conceivable that this could influence the metabolism, or, as discussed earlier, the thickening of the wall.

4. *Nervous factors*

The sympathetic nerves end in the smooth muscle and their activity leads to contraction of the muscle. It would be better to start, however, at the origin of the nerves and to consider how higher nervous influences might work to increase the blood pressure. It has been known for a long time that activity of the higher nervous centres in the brain has an effect on the arterial pressure. A whole school of thought, following the work of Pavlov and the concept of the conditioned reflex, has felt that over-activity of the higher nervous centres in response to environmental stress causes the rise of arterial pressure which may finally lead to persistent hypertension. There is no doubt that emotional factors influence the vascular system (eg, blushing), but that they lead to persistent hypertension is not as certain. Much is made of the rats that became hypertensive when deliberately exposed to the supposedly unpleasant stimulus of a high-pitched sound, but more evidence needs to be produced to substantiate this effect. Some interesting studies have been made by Brod and Barcroft showing the effect on arterial pressure and blood-flow through various organs when mental arithmetic is done under conditions of stress. Brod has made the point that the pattern of response is noticeably similar to that which he has observed in

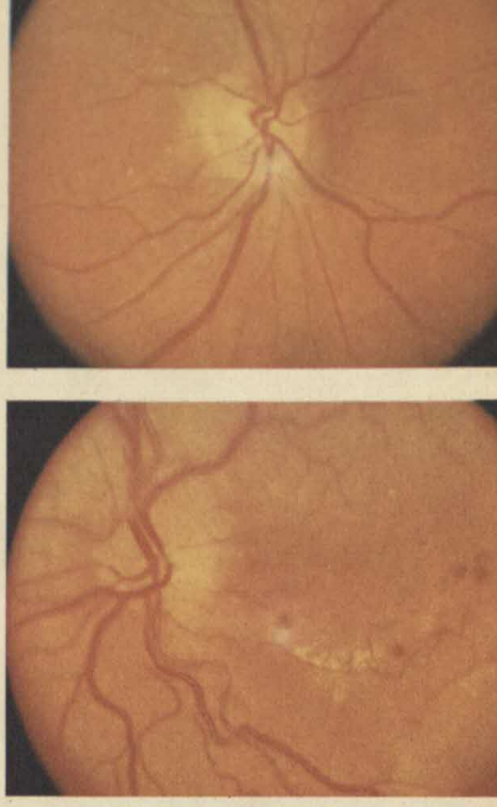


Fig. 4. Photographs of the retina: above, the optic nerve is shown in the centre, together with narrow arteries and wide veins. Below, increased sinuosity of retinal arteries due to hypertension.

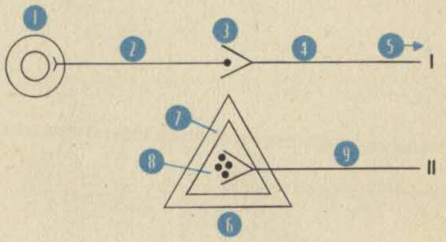


Fig. 5. Schematic representation of a ganglion of the sympathetic system and of the suprarenal medulla, with afferent and efferent nerve fibres. 1, direction of brain; 2, afferent motor-nerve fibre; 3, ganglion, with a synapse where adrenalin and noradrenalin secretion occurs; 4, efferent nerve fibre which transmits nerve impulses to the blood vessel (5). At 6, nerve fibre leading to the suprarenal capsule (7); 8, suprarenal cortex; 9, suprarenal medulla, in which nervous excitation causes secretion of adrenalin and noradrenalin.

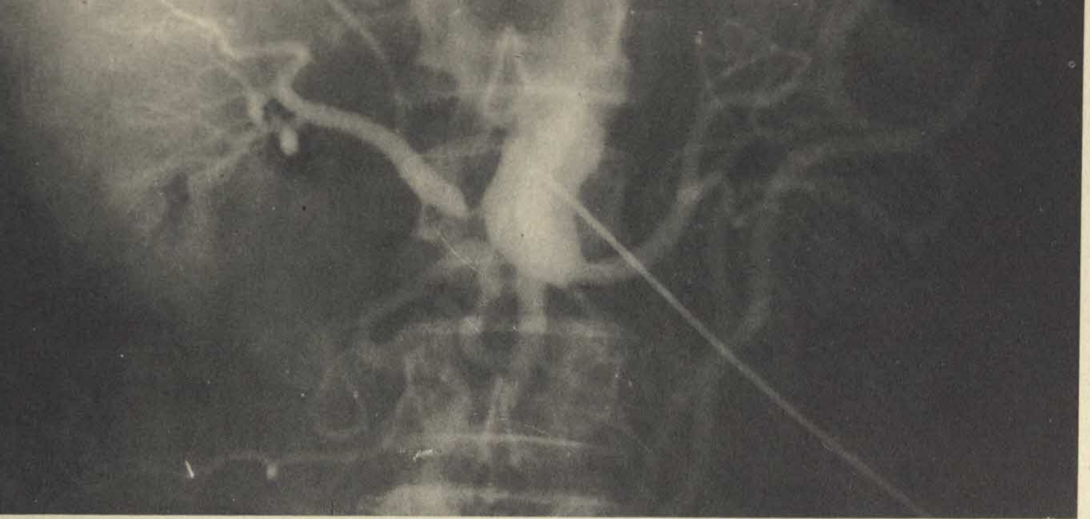


Fig. 6. Aorta of patient with serious hypertension, a radiograph obtained by introducing a catheter into the aorta and injecting an opaque substance. In the centre, the aorta with the catheter needle. Left, main renal artery (right artery of patient) with a characteristic stenosis where it begins. In comparison, note the normal origin of the left renal artery (on the right in the photograph). The lower part of the aorta is blocked by an atheroma analagous to that of the right renal artery.

certain patients with high arterial pressure in its supposedly early stages. How these effects are produced is not certain, but the vasomotor centres in the brain could presumably cause over-activity of the sympathetic vasoconstrictor fibres to the arterioles and increase the resistance. As the cardiac output can be increased also by such sympathetic nervous activity, the arterial pressure would be expected to rise. The sympathetic nerve fibres contain a substance called noradrenalin, which is a powerful constrictor of the arterial smooth muscle, and it is the liberation of this substance at the nerve ending which finally determines the arterial constriction. Clearly, if the action of this substance on the vessel-wall were increased in some way by a metabolic factor or another substance present in patients with high arterial pressure, then this would be a cause of high arterial pressure. No such substance or effect has been described in hypertension as yet.

5. *Endocrine effects*

(a) *Suprarenal medulla:* In the centre of the suprarenal gland there is some dark tissue known as chromaffin because of its histological staining characteristics. It contains adrenalin and noradrenalin in large amounts which are released into the circulation when the splanchnic sympathetic nerves are stimulated. There is a similar but much less marked release into the circulation from other sympathetic nerve endings, and this emphasizes the interesting anatomical fact that the medulla is merely a condensed post-ganglionic sympathetic fibre.

In man, tumours, known as phaeochromocytomas, and which are usually benign, arise in the medulla. They secrete large amounts of adrenalin and noradrenalin, which cause sharp rises of pressure by direct vasoconstriction of the arterioles, and the patient sweats. Removal of the tumours restores normal blood pressure.

This is the clearest example of a natural vasoconstrictor substance in the body causing severe hypertension. The circulatory effects have been well studied and it is the only example of high arterial pressure which has been completely elucidated.

(b) *Cortex:* The suprarenal cortex produces important steroid hormones which are essential for the maintenance of life. Their main effect is on carbohydrate and protein metabolism (hydrocortisone), and on the maintenance of water and electrolyte balance, mainly by an action on the kidney (aldosterone). However, over-activity caused either by the growth of a tumour or merely hyperplasia will lead to over-production of these and other hormones, and high arterial pressure results. Other effects are to be noted in patients with this condition (fig. 3, an example of Cushing's syndrome, due mainly to over-production of hydrocortisone and androgens), but a high arterial pressure is common. The way in which this effect is ultimately exerted is not known, but it can be reversed by cutting out the tumour or the suprarenals themselves.

In most patients with high arterial pressure there are no obvious signs or biochemical evidence of over-activity of the suprarenal cortex, and such cases are rare.

Redistribution of water and electrolytes

It is frequently observed in patients with high arterial pressure that their metabolism of water and salt is different. They excrete more salt and water via the kidneys than is normally excreted, and though the distribution of water and salt in the body is sometimes different, it is uncertain what relation this has to high arterial pressure. Like so many phenomena in high arterial pressure, they are an effect, not a cause. This does lead, however, to a consideration of the role of the kidney in high blood pressure, since this is the most important regulating organ for these substances. It has been known since the early years of the last century that there is an association between disease of the kidneys and high blood pressure. The famous physician, Richard Bright, was the first to investigate this association. The history of it has four important aspects which lie behind an understanding of the role of the kidney. The first is Bright's description of the shrunken kidney of chronic nephritis, which bears his name, and the enlargement of the heart which accompanies the disease. The

(2) *The* glomerulus *is anatomically like a cup for ultrafiltration of the blood. The protein and cell-free ultrafiltrate passes into the tubules where it is modified and emerges as urine. The diseases of the kidney associated with high arterial pressure are numerous, varying from tumours to tuberculosis. I believe that the common factor which links them all is interference with the kidney blood supply. This mechanism is most clearly shown by obstruction of the main kidney artery, but it applies equally to obstruction by disease processes within the kidney.*

second is the discovery by Tigerstedt and Bergman of the kidney enzyme 'renin', which raises the blood pressure on intravenous injection. The third is Goldblatt's demonstration in an animal that narrowing the artery to one kidney by a ligature leads to high blood pressure. The fourth is the demonstration by Butler that removal of a diseased kidney in man leads to a cure of high arterial pressure if the remaining kidney is normal. Putting all these observations together, it seemed clear that interference with the blood supply to the kidney caused a substance to be released into the circulation which caused high arterial pressure. Removal of the kidney, and therefore of the source of the substance, cured the hypertension. Examples of disease causing such an obstruction to the blood supply of the human kidney are many and illustrations are given in figs 7 and 8. These show a block in the main renal artery due to atheroma (cholesterol deposition plus fibrosis in the wall). This interference with blood flow can be proved by studying the composition of urine collected separately from the two kidneys and showing that removing or by-passing the block will cure the high blood pressure. The effects on the kidney of a lowered blood supply have been extensively studied, but the mechanism of hypertension is still unknown.[2] As renin is an enzyme present in the cortex of the kidney, situated close to the glomeruli[3] (the filtering parts which depend so much on the arterial pressure for their adequate function), it seems obvious that this is the substance which is released when the blood supply to the kidney is reduced. It is an enzymic pressor substance which combines with a protein substrate in the plasma to produce a peptide of known structure called angiotensin. It is this which raises the arterial pressure by directly constricting the arterial wall. However, efforts to demonstrate renin and angiotensin in renal disease with high arterial pressure have had conflicting results and adequate proof is not yet forthcoming. Angiotensin certainly readily raises the arterial pressure in man when injected intravenously in small amounts (1–5 μg/min).

Many would like to implicate the suprarenal in this story and suggest that disease of the kidney leads in some way to the release of adrenal steroid hormones which cause high blood pressure. This would make the mechanism similar to that of some cases of adrenal over-activity discussed previously. There is clearly some relation, but it is not a straightforward causal connection, and there is much to suggest that it is a change due to the high arterial pressure itself.

Therefore the biggest challenge in hypertension is the role of the kidney, and a solution of this problem would solve a large part of the whole problem of high arterial pressure, since the kidney is so commonly implicated in this condition.

The main impression on looking into this problem is of the multiplicity of factors which can affect the blood pressure; sometimes one predominates, sometimes another. Except for certain rare illnesses like phaeochromocytoma, no convincing full account has been given of any one cause of high arterial pressure in man or animal, and the challenge remains.

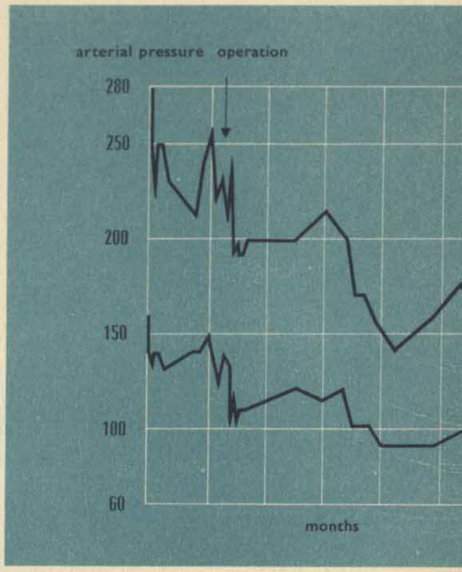


Fig. 7. Diagram showing fall of arterial pressure after excision of a partial obstruction of a renal artery. 1, curve corresponding to the systole (maximum: fall from 250 to 140); 2, curve corresponding to the diastole (minimum: from 160 to 90).

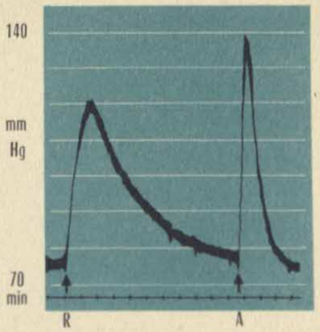
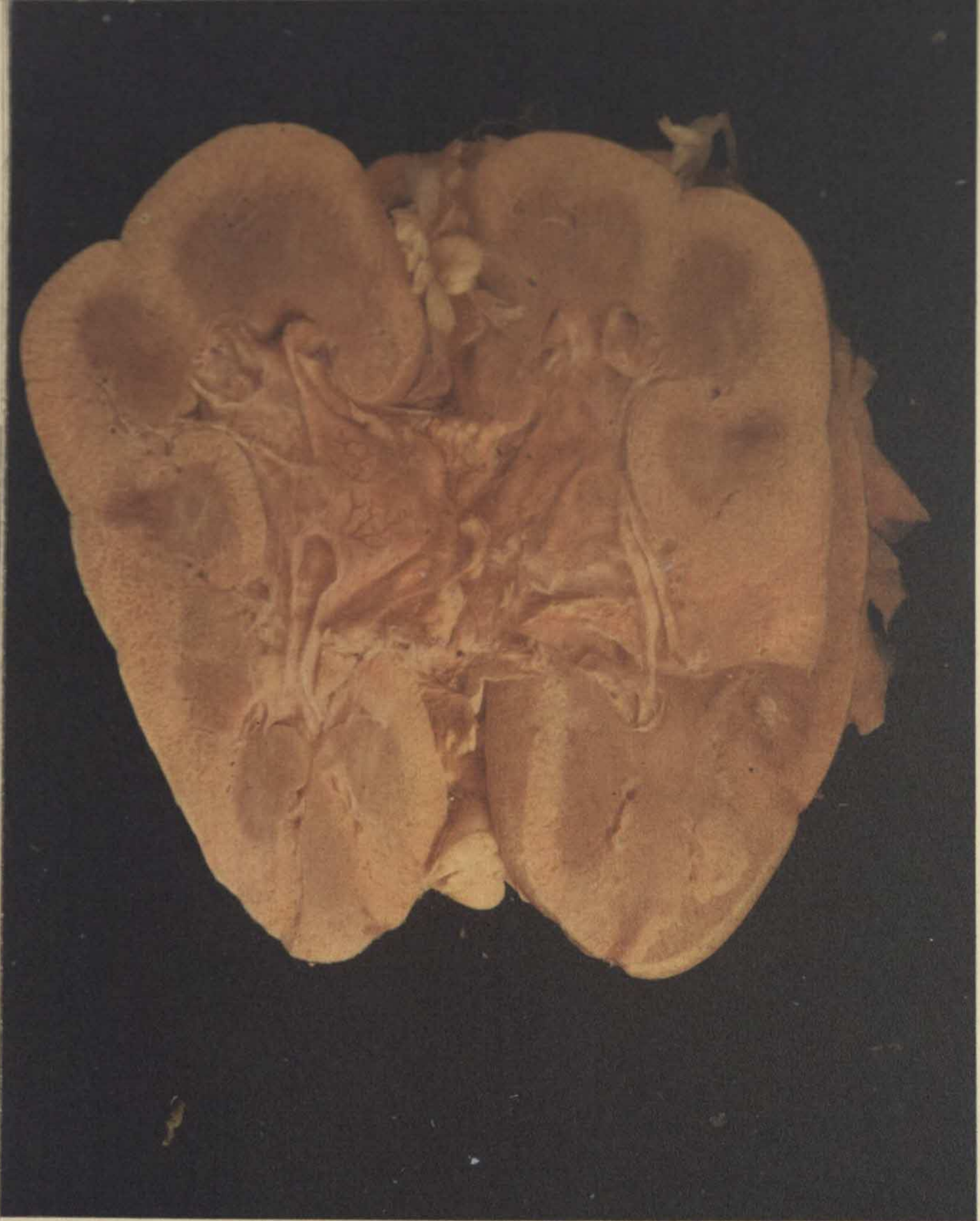
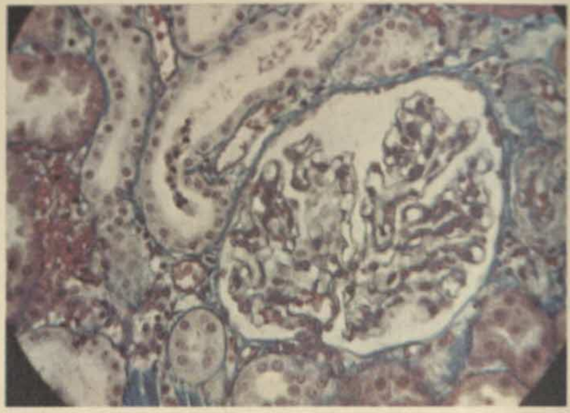
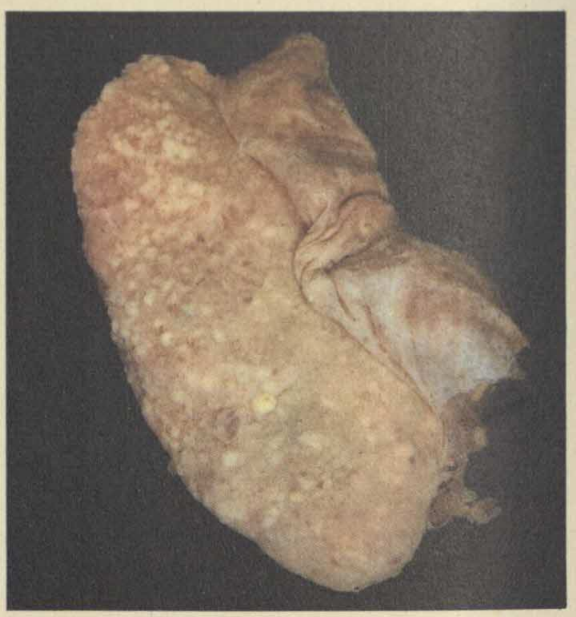


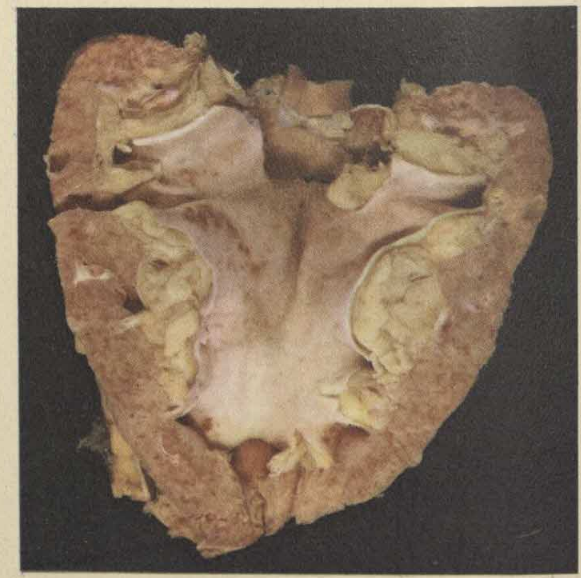
Fig. 8. Effects of intravenous injection of renin (R) and angiotensin (A) on the blood pressure of an anaesthetized rat. With renin the rise of blood pressure is slow; with angiotensin it is very rapid and violent.





A renal glomerulus: the tuft of capillaries where urine is formed by filtration, and whose unimpaired structure is thus essential for the proper functioning of the kidney.





Disturbance of the renal system may have drastic consequences, in view of the regulatory functions for which the kidneys are responsible, which affect the whole of the organism. The picture above is of a normal kidney bisected and opened out to show its structure. Towards the edges are glomeruli surrounding bundles of excretory ducts which lead to the renal pelvis. Above and on the right, a section of a glomerulus.

The kidneys may be the seat of an inflammatory process called nephritis; the lower illustrations on the right show the external appearance and internal structure of a kidney affected by chronic hypertensive nephritis. The whitish nodules on the surface are the scars of nephritic lesions that have destroyed nearly the whole of the renal parenchyma. In the bottom picture, note how much of the kidney has disappeared as a result of this destruction. (Preparation by Serrurier. Photos Lod).

The renal system

Marcel LEGRAIN

The kidneys are essential to the control of the body's internal environment and the maintenance of life. The structure and functions of the kidneys are well known, and it is therefore possible to correct to some extent effects of functional deficiencies in them. In this chapter, Dr Legrain deals with nephritis and the 'artificial kidney', which temporarily takes over the work of the patient's own kidney and may enable him to survive an otherwise fatal illness.

Anatomically, the renal system consists of the two kidneys. Each is a solid organ, weighing about 150 grams, situated below the diaphragm, behind the posterior parietal peritoneum, and in front of the lumbar muscles. The kidneys are connected to the urinary bladder by two flexible and contractile tubes, known as the ureters.

Histologically, the kidney consists of a million *nephrons*, each of which is an independent functional unit of complex structure, made up of two basic elements: a *glomerulus* and a *tubule*.[1] The diameter of a tubule is between 20 and 50μ and its length is about 50 mm, so that the total length of all the tubules is about 50 km (31 miles).

The epithelium at the blind end of the tubule covers a tuft of capillaries and forms the glomerulus. The other end of the tubule opens into a collecting tubule which conveys the urine to the renal pelvis and thence by way of a ureter to the bladder.

The physiological function of the kidneys is to form urine. Contrary to popular belief, their purpose is not to eliminate end-products of metabolism, such as urea, but to maintain the balance of body fluids by regulating the 'output' according to the 'input'. The kidneys ensure homoeostasis.[2] They ensure that constancy of the body's internal environment which, in the words of Claude Bernard, is 'essential for free and independent life'. The American physiologist, Homer Smith, expressed the same idea more vividly: 'Superficially the function of the kidney can be considered to be the secretion of urine, but on a deeper plane it may be said that the kidneys are the basis of thought'. This is no exaggeration, for certain mental disturbances are related not to a raised level of blood urea, but to more complex and variable disorders of the internal environment, due to impairment of renal function.

Exploration of renal function

Detailed examination of the kidney's functions is now possible. Little by little the nephron is yielding up its secrets, through the introduction of more and more refined methods of investigation. Ever since Richard Bright, in 1827, discovered the significance of albuminuria[3] in renal disease, the great importance of studying the urine has been recognized. *Chemical* examination includes qualitative tests and estimation of both normal (urea, electrolytes, etc) and abnormal (glucose, albumin, etc) constituents of urine. *Cytology* reveals the presence or absence in the urinary sediment[4] of abnormalities such as microscopic blood or pus. *Bacteriology* shows whether the urine is sterile, or infected by germs such as colon bacilli, staphylococci, etc.

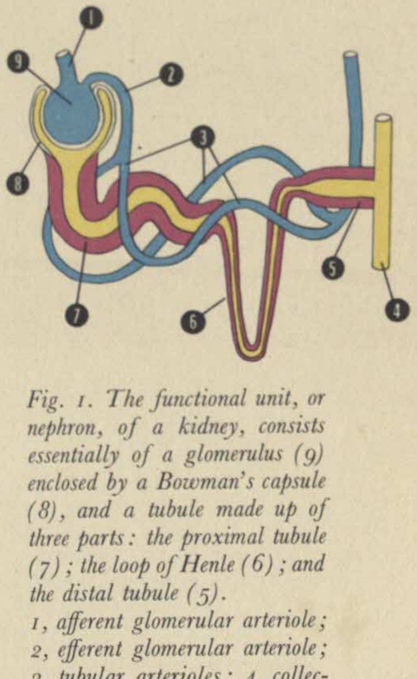


Fig. 1. The functional unit, or nephron, of a kidney, consists essentially of a glomerulus (9) enclosed by a Bowman's capsule (8), and a tubule made up of three parts: the proximal tubule (7); the loop of Henle (6); and the distal tubule (5).

1, afferent glomerular arteriole; 2, efferent glomerular arteriole; 3, tubular arterioles; 4, collecting tubule (leading to the bladder).

Blood tests show various disturbances in the chemical composition of the body fluids, such as a rise in blood urea, 'imbalance' in the organism's electrolyte equilibrium, due to impaired renal function, etc. The levels of a given substance in the blood and urine may be compared in order to estimate the kidney's ability to 'clear' the substance from the blood. 'Clearance' is defined as the number of millilitres of plasma from which a substance can be eliminated by the kidneys per minute. It can be measured for any substance present in the blood and excreted in the urine by the formula:

$$\frac{U \times V}{P}$$

where U and P represent the concentrations of the substance in urine and blood respectively, and V the rate of urine secretion.

X-ray examination usually supplements these chemical tests. Provided that renal function is shown to be adequate, an intravenous injection of an iodized contrast medium can be administered: this is known as intravenous urography. In renal insufficiency, the opaque substance may be injected instead through catheters inserted into the ureters: this method is called pyelography. In exceptional cases it is useful to make the renal blood vessels opaque, and this can be done by means of a needle or catheter passed into the aorta at the level of the renal arteries: the X-ray photographs thus obtained are known as renal arteriograms.

The biological and anatomical study of the kidney is completed by histology. It is now possible, under local anaesthesia, to take a fragment of kidney from a conscious patient for microscopic examination; this is done by means of a specially designed needle, or trocar.

Pathology

The study of kidney diseases is called nephrology. Such diseases are often discovered by finding albuminuria during a routine examination of the urine.

Pain, which is known as renal colic,[5] is variable. It usually occurs in the small of the back and is sometimes slight, sometimes acute. Sometimes the amount of urine is altered: reduction is known as oliguria and complete suppression as anuria. The start of some kidney diseases is indicated by the passage of blood (haematuria).

Oedema, or dropsy, is the clinical manifestation of excessive hydration of the tissues, and results from a retention of sodium in the body. It is one of the symptoms of the nephrotic syndrome.[6] Hypertension is common in many types of nephritis, but its cause is still obscure.

There are many causes of kidney disease. They may be congenital, eg, malformation of the kidney, but are more often a result of poisoning, infection, or inflammation. Many kidney diseases originate from an infection of the nose or throat, usually streptococcal, or urinary, but the cause of most of them is still unknown.

Like diseases of other organs, in those of the kidney a distinction must be made between diseases that are localized and those that affect the whole organ. The generalized affections are usually grouped together under the name of nephritis. Acute nephritis may be serious, but there is often a complete recovery from it. Chronic nephritis usually runs a very slow course, but sooner or later signs of renal insufficiency appear, resulting in the condition known as uraemia,[7] because the level of blood urea is always raised.

Localized kidney disease never results in renal insufficiency, because a small portion of healthy renal tissue (about a third of one kidney) is sufficient for normal health. The condition may be benign, as in the case of a cyst, or serious as in cancer. Sometimes it is a local indication of a generalized disease, such as tuberculosis.

Disorders of the upper urinary tract are usually included among renal diseases: eg, congenital or acquired malformations, such as dilation of the renal pelvis (hydronephrosis), and stone formation, due to precipitation of calcium salts (oxalate, phosphate) in the urinary tract, or of organic substances (uric acid, cystine, etc).

Treatment

Treatment of renal disease may have several aims. In some cases, it is possible to strike at the root of the trouble and effect either a partial or a complete cure, as, for example, by the eradication of a urinary infection by antibiotics, or the surgical relief of a constriction between the renal pelvis and the ureter, which may have led to dilation of the underlying kidney.

Sometimes, the most effective treatment is the radical step of the complete or partial removal of a kidney. But this, of course, must never be undertaken without a careful study of the functional efficiency of the other kidney. With the progress of medical treatment, eg, chemotherapy for tuberculosis, such operations have become less common.

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(1) *For further information, see the chapter on The Kidney by Jean Hamburger, in Volume 5.*

(2) Homoeostasis: *the maintenance at their proper levels of the physiological constants, such as body temperature, blood pressure, and the composition of the blood plasma. The chapter mentioned above gives further details.*

(3) Albuminuria: *this common term is often used incorrectly. It denotes any kind of* proteinuria, *whether the urinary protein is in fact albumin or globulin, or both.*

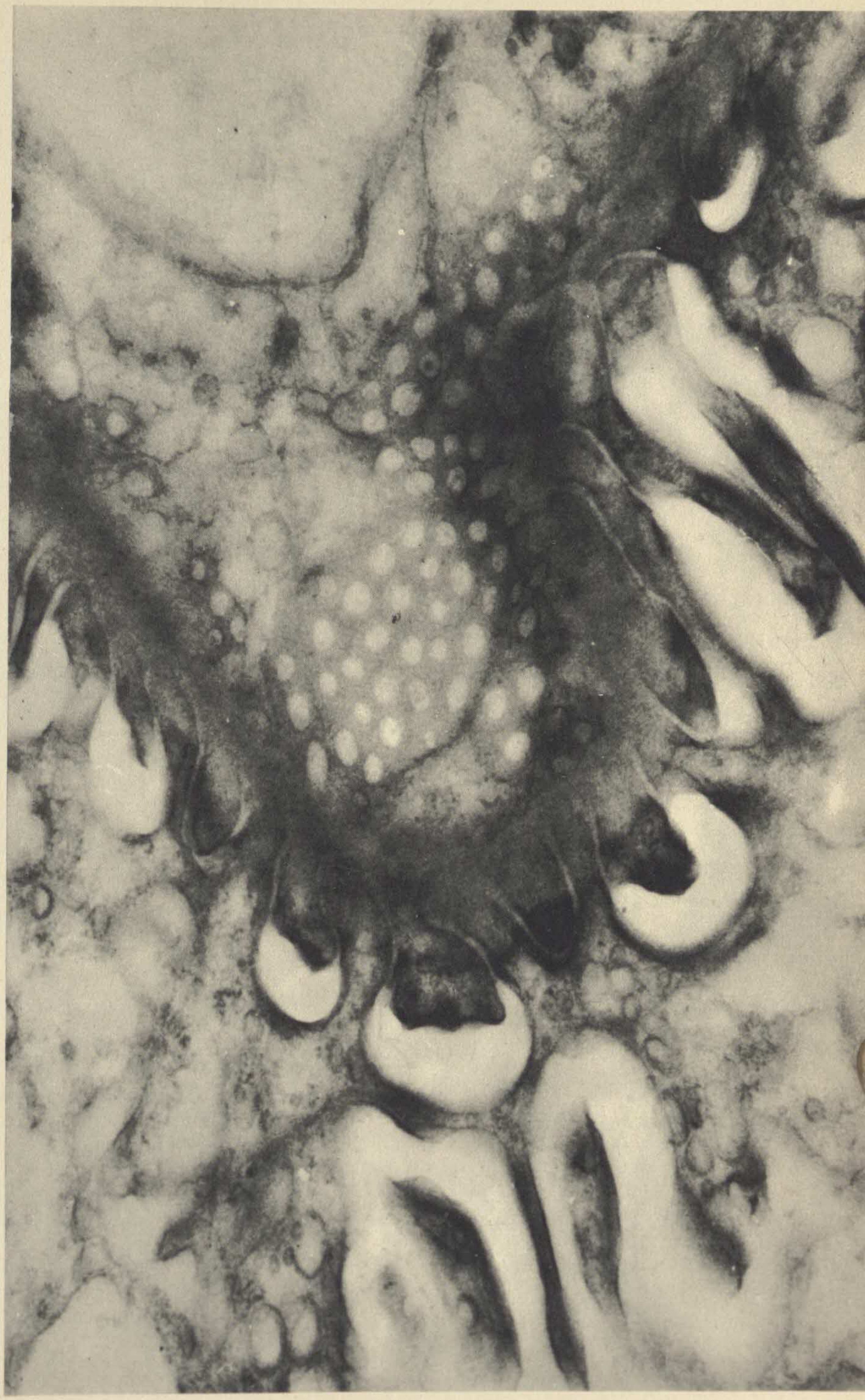
(4) *Microscopic examination of a* urinary sediment, *separated from the urine by centrifuge, shows how much of it consists of formed elements, such as red and white blood corpuscles, other cells, and casts.*

(5) Renal colic: *an attack of pain, often extremely severe, associated with distension of the urinary tract, usually owing to obstruction of a ureter. It is a common symptom of renal calculus, or stone.*

(6) Nephrotic syndrome: *this is characterized by massive proteinuria, oedema, and a reduction in the plasma proteins and an increase in the lipids. It is the result of damage to the glomerular filter, which allow large quantities of protein to escape into the urine.*

(7) Uraemia: *the group of symptoms of renal insufficiency that accompany the retention in the body of substances normally excreted in the urine, such as urea. The symptoms of uraemia are not, however, the direct result of a high level of urea in the blood.*

The glomerulus acts as a filter which lets water and electrolytes through, but holds back cells and large molecules, eg, red blood cells and proteins. This tangential section of a part of the glomerular tuft, greatly magnified by an electron microscope, shows the complicated structure of the filter. Its anatomical arrangement provides a very large filtration area, and it is inflammation of this multicellular surface that leads to the thickening and hardening characteristic of glomerular nephritis. (Photo Dr Legrain).



In many cases, although there may be no possibility of cure, treatment can mitigate the serious metabolic consequences of renal insufficiency.

Diet plays an important part in the treatment of nephritis; a diet must be worked out individually for each patient, and for each stage of the disease.

Sodium restriction, which is necessary in cases of oedema, is of no value in most other forms of renal diseases, or for people suffering from albuminuria alone. In 'salt-losing' types of nephritis, it is often necessary to add salt to the diet.

Protein restriction is essential when renal insufficiency leads to the retention of nitrogenous substances. The extent to which it should be restricted must depend on the excretion of urea; it can be completely restricted only for short periods of time. When treatment has to be given over a long period, the daily intake of protein must not be less than half a gram per kilogram of body-weight.

The artificial kidney

Occasionally, the kidneys temporarily fail completely and the patient must be tided over this critical period. For this purpose the artificial kidney is of great value. Several types are in use, but they all work on the principle of dialysis between the patient's blood and a suitable solution (resembling Ringer's) across a cellophane membrane.

Within a few hours, 'extrarenal purification' of the blood is achieved. The procedure can be repeated as required, and enables the patient's condition to be maintained pending the recovery of renal function.

The refractory nature of many forms of nephritis, and the fact that we have two kidneys, explains why the kidney is the first organ that doctors have tried to transplant from one person to another. So far, the attempts have been successful only between twins. Renal grafts are still a dream, but also an aim of research.

Glands of internal secretion

Lucien de GENNES and Henri BRICAIRE

The hormones poured into the blood in infinitesimal quantity by the glands of internal secretion are the main modulators of intracellular chemical reactions. No gland can function without the others: either its effect is balanced by the moderating action of another gland, or its hormones cannot be liberated unless activated by an internal secretion from elsewhere. Such is the complexity of endocrinology, the science of internal secretions and a fundamental discipline of medicine, very firmly based on all the biological sciences.

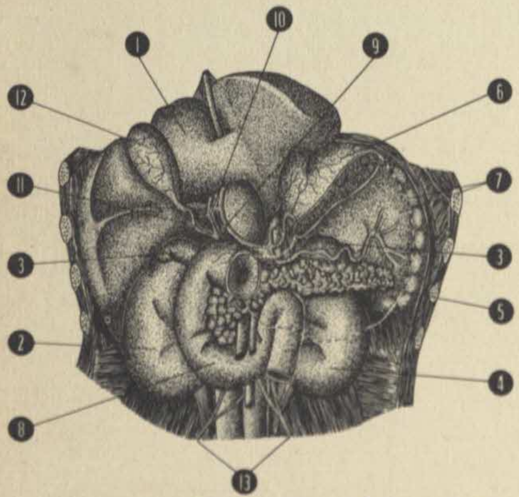


Fig. 1. General view of the various glands of internal secretion in the central region of the body: the right suprarenal capsule (3) above the right kidney (2), and (5) the pancreas. 1, lower surface of the liver; 4, left kidney (surmounted by the left suprarenal, capsule scarcely visible); 6, upper part of the stomach; 7, spleen; 8, duodenum; 9, hepatic portal vein; 10, bile-duct; 11, cystic duct; 12, gall-bladder; 13, spermatic vessels.

Glands of internal secretion, or endocrine glands, are defined by the fact that their secretion, instead of being collected into a discharging channel, is poured out directly into the blood by means of capillary vessels that surround their cells. In this way the secretion is diffused throughout the whole body and regulates its activities.

Before the time of Claude Bernard and Brown-Séquard, it was not believed that these groups of cells, without an outlet duct, played an important role and that their secretions could, as we now know that they can, direct most of the important functions of the body.

William Bayliss was the first to give these subtle substances secreted by the endocrine glands the name of hormones. Produced in these glands and in infinitesimal quantities, the functions of hormones are to activate and control the growth of the human body, the development and function of the various organs, the regulation of respiratory exchanges, the mechanism of cellular exchanges, and the movements of water, sugars, sodium, calcium and potassium in the body; in short, the main constituents of the liquids on which life depends. The role of these hormones is therefore accepted nowadays as being of great importance, since they determine not only our organic and sexual life, but also some part of our emotions, our behaviour, and doubtless our intellectual activities.

As a result of the astonishing discoveries of the last few years, the composition, structure and function of most of these chemical messengers are now understood. We know the cells from which they originate and the paths that they follow, since the study of hormones marked by radio-active elements enables us to follow them step by step anywhere in the body. We know in what quantity they are active; it is infinitely small and may be effective, as with adrenalin, for instance, at a millionth of a milligram.

Hormonal chemistry has succeeded in isolating, establishing the structural formulae, and reproducing by synthesis the greater part of these subtle substances which, for therapeutic purposes, are extremely powerful and astonishingly precise.

The very success of these discoveries makes endocrinology a dangerous science and its application a delicate task. Endocrine treatment no longer consists of the simple ingestion of gland extracts. With the pure hormones obtained today by extraction or synthesis, the physician is handling explosive material that may equally well produce a beneficial result or lead to disaster. Endocrinology should be practised only by those possessing a discernment that requires profound knowledge and long experience.

The solution of certain problems, such as those of cell division, associated with the origin of malignant tumours, depends partly on a better understanding of hormonal factors. This fact strongly emphasizes the enormous importance of these discoveries; new facts are added every day and are making endocrinology one of the most highly perfected branches of biological science.

The endocrine system

The endocrine system is mainly composed of certain well-known glands: the pituitary, thyroid, parathyroids, suprarenals, and genital glands (ovaries in women and testicles in men). But besides these fundamental components, the functions of which are now clearly elucidated, the body has a series of disseminated centres of internal secretion of no less importance than that of the main glands.

The *islets of Langerhans* are small microscopic groups of cells scattered in the substance of the pancreas where they secrete insulin, the hormone that regulates the sugars of the body. Certain cells of the intestine, liver, vessels and nerves are other examples of these centres of internal secretion. There are also elements and nerve centres situated in the brain substance itself, that have an internal secretion that controls the regulation of water in the body and many other functions.

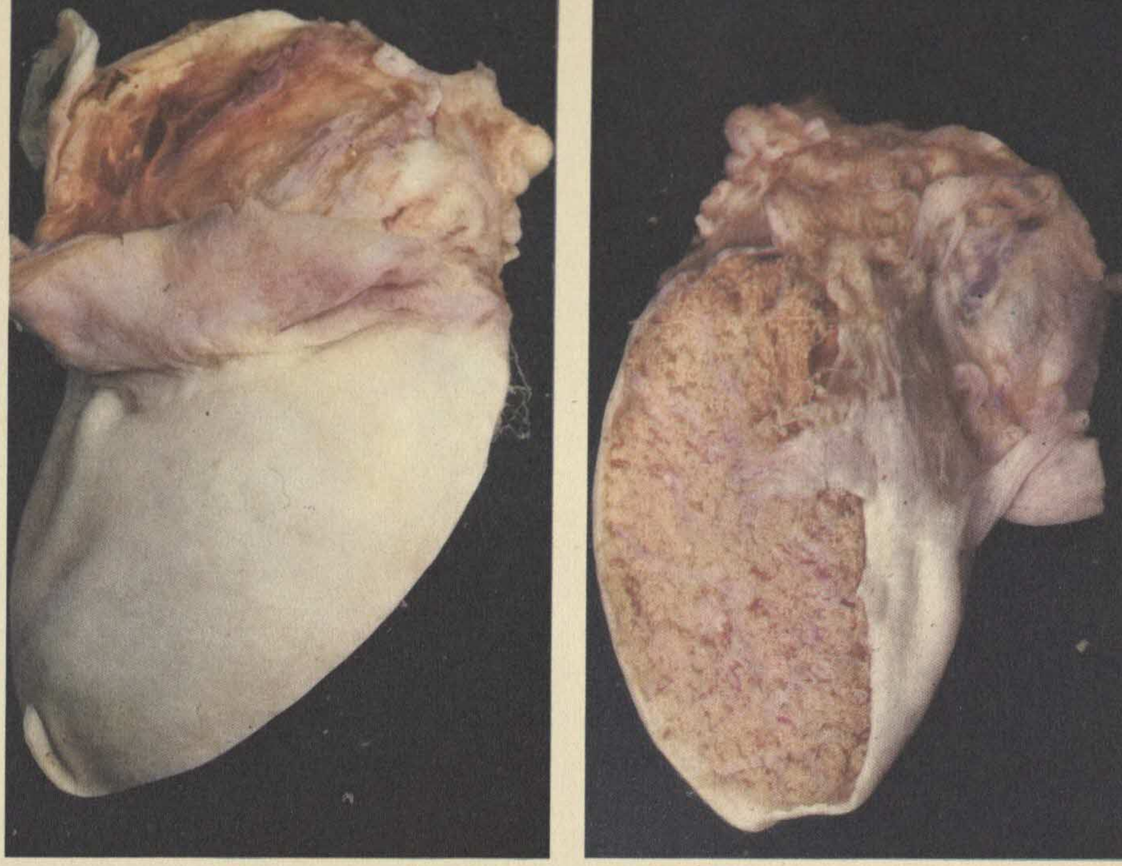
Certain temporary formations, such as the corpus luteum of the ovary, which is formed each month after ovulation, or the placenta, which accompanies pregnancy, have very important internal secretions.

Such is the endocrine system in its totality. Each of the glands has its own secretion and its own specific function. Each reacts on other endocrine glands and their secretions.

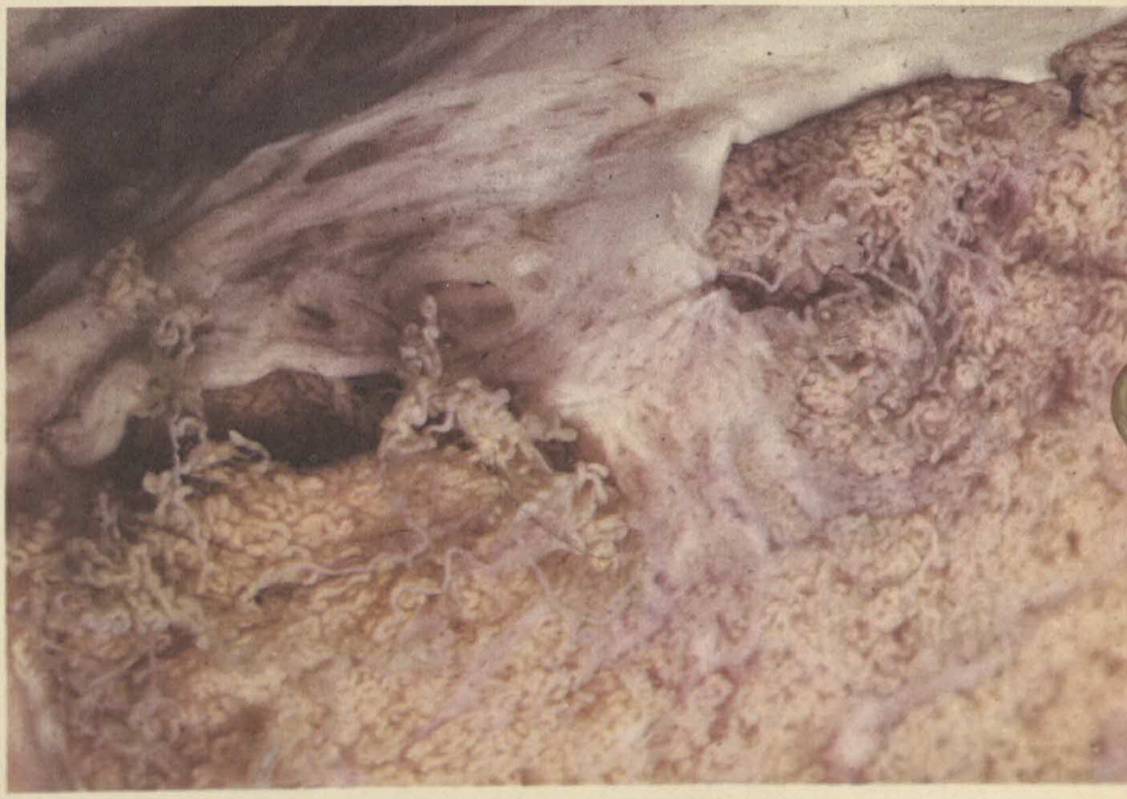
These activities are carried out more especially by the hormones, but also by the mediation of the nervous system, which receives stimulations and in turn reacts on glandular functions and on the production of these hormones.

The pituitary

The pituitary, situated under the brain in a bony niche at the base of the skull, is remarkably well protected. It is made up of two distinct parts.



The genital glands, apart from their reproductive function, possess an important endocrine function: they secrete hormones that control secondary sexual characters. Above, external view and section of testis of a healthy male. Below, detail of the tubular structure of the adult testis; note the white fibrous tissue that covers this gland.



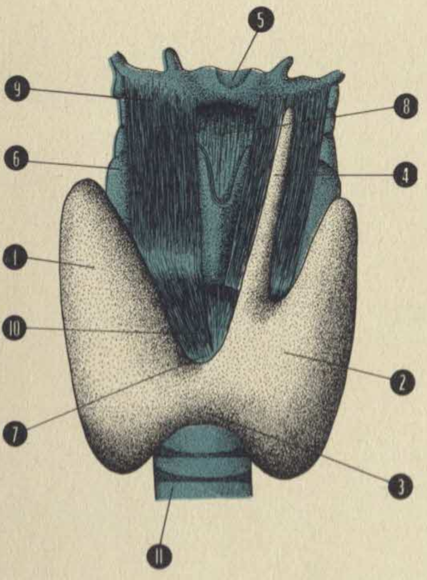


Fig. 2. Anterior view of the thyroid gland in position on the larynx. 1 and 2, right and left lobes; 3, thyroid isthmus; 4, pyramidal lobe; 5, hyoid bone; 6, thyroid cartilage; 7, cricoid cartilage; 8, hyothyroid membrane; 9, thyrohyoid muscle; 10, cricothyroid muscle; 11, trachea.

The posterior lobe is attached to the brain by the pituitary stalk. This is an extension of the nervous system and according to present-day views it plays the part of a vector for the transmission of secretions arising in centres in the brain, rather than that of a gland with its own secretion.

The anterior lobe, larger, and fused on to the posterior lobe, is a gland of great importance. It secretes a *somatotrophic* hormone, responsible essentially for the growth of the body; and a series of hormones called *stimulins*, the functions of which are to develop and activate the other main endocrine glands—such as the thyroid (thyrotrophic hormone or TSH), the cortical suprarenal glands (corticotrophic hormone or ACTH) and the genital glands, ovaries or testicles (gonadotrophic hormones or gonadotrophins).

These peripheral glands, stimulated by the action of the pituitary stimulins, react by increasing the secretion of their own hormones. When these are found in excess in the body, this excess itself slows down and blocks the stimulin secretion of the pituitary; in other words, the entire hormonal apparatus functions cybernetically, like a thermostat.

The anterior pituitary is the most important gland in the body, since it controls man's growth, as well as that of the various organs and, by the action of its stimulins, it controls the functions of most of the other glands of the endocrine system. Consequently, it is easy to see that lesions of the anterior pituitary or disturbances in its function are of great importance.

When any type of lesion (a tumour, compression, a wound or an infection) attacks the pituitary and diminishes its secretions, the functions of the tributary glands (the genital thyroid, and suprarenal glands) are disturbed, since they are no longer excited by the pituitary stimulins. In a child or an adolescent, growth is retarded; the genital organs atrophy or do not develop. In the adult, sexual function disappears, menstruation ceases and secondary characters (hairiness, male voice and sexual desire) vanish, resulting in total impotence and permanent sterility. At the same time, signs of thyroid insufficiency appear. Intellectual activities are slowed down, thought-processes are lethargic, reactions are diminished, and memory becomes defective, although judgement usually remains unimpaired.

Suprarenal insufficiency, caused by this pituitary deficiency, is shown by increasing fatigue, inability to make any effort, and a decrease in blood-pressure; at the same time, analysis of the hormonal contents of the urine shows a heavy drop in the level of cortico-suprarenal hormones, the secretion of which is no longer activated by stimulins.

All these symptoms of pituitary insufficiency are often explained by the existence of a tangible and sometimes excisable lesion, but there are numerous cases where no lesion of the pituitary itself is to be found. The pituitary, however, is not completely autonomous, and its function is dominated by a series of nervous impulses coming from the base of the brain, especially from an important part of it called the diencephalon.

The *diencephalon*, linked by a series of connections, to the rest of the brain, is in fact a kind of cross-roads where stimuli from the whole body and from all emotive reactions meet and where, through its mediation, they act on the pituitary and its glandular secretions. The majority of psychosomatic illnesses, which have such a strong influence on the functions of the endocrine system, can be explained by the active diencephalic centres.

When, on the other hand, the anterior pituitary is affected by a hypertrophic lesion, such as a tumour which multiplies the number of cells and their secretion to excess, then we witness the appearance of a hyperfunction syndrome.

It is known (somewhat empirically) that there are in the anterior pituitary three types of cells distinguished by their reaction to different stains. There are eosinophil cells which appear to be responsible for the secretion of growth-promoting hormone; basophil cells which appear to govern the secretion of stimulins; and neutral cells (or chromophobes), the action of which is not well defined.

When a tumour consisting of an eosinophil cells increases the number of these cells in excess, and also increases their secretion, growth disturbances occur, characterized by gigantism in a young person with unfused epiphyses, or, in an adult incapable of growing any further, by the striking deformations of acromegaly. The deformed aspect and sometimes monstrous appearance of these victims of acromegaly is due to an excess of growth-promoting hormone.

This hormone which cannot yet be reproduced by synthesis, has now recently been extracted from the anterior lobe of the pituitary in a pure state. It is responsible for multiple effects on growth and also on the regulation of phosphorus and sugar metabolism.

It is efficacious in man, provided that it has been extracted from a human pituitary. Pituitary banks have therefore been established, and pituitary glands that have been removed at postmortem examinations or during operations are stocked and prepared for therapeutic use. So an injectable hormone is now available which can make a human being grow.

This is only one example of the activity of the anterior pituitary. When an excess of secretion involves the basophil cells, which secrete the pituitary stimulins, grave symptoms, which are called Cushing's syndrome, develop. These symptoms are due to an exaggeration of the cortical suprarenal functions, leading to a great excess of cortisone secretion and characterized by an abnormal distribution of fat, serious arterial hypertension, diabetes, excessive hairiness, decalcification of the bones, and progressive muscular atrophy. These extremely grave symptoms disappear if the pituitary tumour is suppressed or if the suprarenals are removed, these being the operative intermediaries in this excess of pituitary stimulins.

The posterior lobe of the pituitary, an outgrowth from the brain, produces no secretion of its own and serves as a vector for those hormones produced in the brain tissue itself. One of these hormones is pitressin, which controls the regulation of water, since it allows it to be reabsorbed by the kidney tubules; a lack of pitressin causes loss of water by the kidney and arouses thirst in order to replace the loss (diabetes insipidus). Another of these hormones is oxytocin which governs the contraction of smooth-muscle fibre in particular, and uterine spasm during birth.

The thyroid gland

The thyroid, a large gland situated in the front of the neck and divided into two lobes, secretes two main hormones, thyroxin and tri-iodothyronin, which regulate calorie exchanges in the body. Previous assessments of this function were based on measurements of respiratory exchanges of oxygen and carbon dioxide (basal metabolism). These increase if secretion is excessive, and vice versa. The mechanism of thyroid functions is, however, based first and foremost on the role of iodine. Any quantity of iodine introduced into the body, whether by mouth or by subcutaneous, intramuscular, or intravenous injection, is stored almost entirely by the thyroid gland.

Some hours after injection or ingestion of radioactive iodine (^{131}I), nearly all this labelled iodine may be found and measured in the thyroid gland by using a Geiger counter, and the rapidity of fixation and elimination can thus be assessed. This enables an exact measurement of thyroid gland activity to be made, and detects hyperfunction or hypofunction diseases. When this gland functions in excess and secretes considerable quantities of thyroid hormone (thyroxin or tri-iodothyronin), it marks the development of a very serious condition known as Basedow's disease, or exophthalmic goitre. This is characterized by the appearance of a throbbing and pulsatile goitre, notable acceleration of heart-beat, nervous disturbances of personality, accompanied by trembling, great loss of weight, and an infinitely varied series of organic disturbances. Before recent discoveries were made, this frequent and serious disease (especially in women) often ended in death. Today it is sufficient to diminish the activity of the thyroid gland, either by almost total excision, or better still, by administration of a sufficient dose of radioactive iodine, for the disease to be mastered in a few days or weeks, and for a cure to be definitely ensured.

It would be a mistake, however, to consider exophthalmic goitre as an exclusively thyroid disease. It is, in fact, often a secondary disease that follows a sudden excess of thyrostimulin, of diencephalic pituitary origin, that sometimes results from an emotional crisis, causing an increase in production of thyroid secretions. This is one of the most striking examples of the interdependence of endocrine glands and of the disorders that may arise from a disturbance of the regulation by the diencephalon and the pituitary.

When the opposite happens, and the function of the thyroid is slowed down, suppressed either because of a direct glandular lesion or because of a deficiency of pituitary stimulins (thyrostimulin) which it needs, a deficiency disease, known as myxoedema, then occurs. It consists of a general slowing down of exchanges between all the functions of the body. The whole skin and face appear to be invaded by a hard oedema. This disturbance appears most often in women at the age of the menopause. The face becomes rounded, the eyelids thicken, the forehead is deeply wrinkled; the nose becomes enlarged, the lips thicken and the ears are swollen. The facial expression is sad, inexpressive and inhibited. The hands are thickened, the fingers swollen, the hair and eyelashes sparse and dry, the skin also dry and without perspiration. The voice becomes

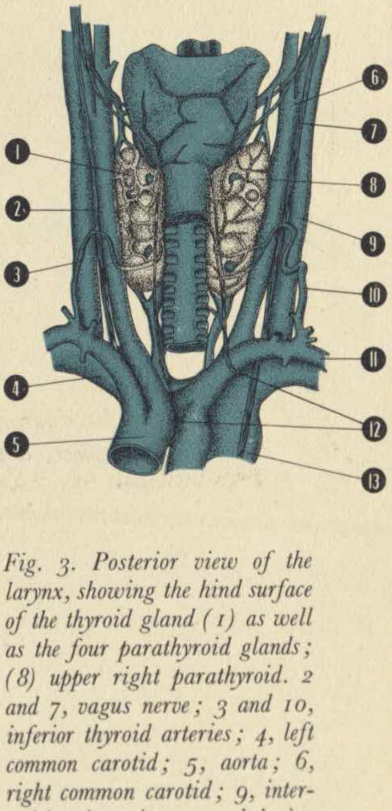
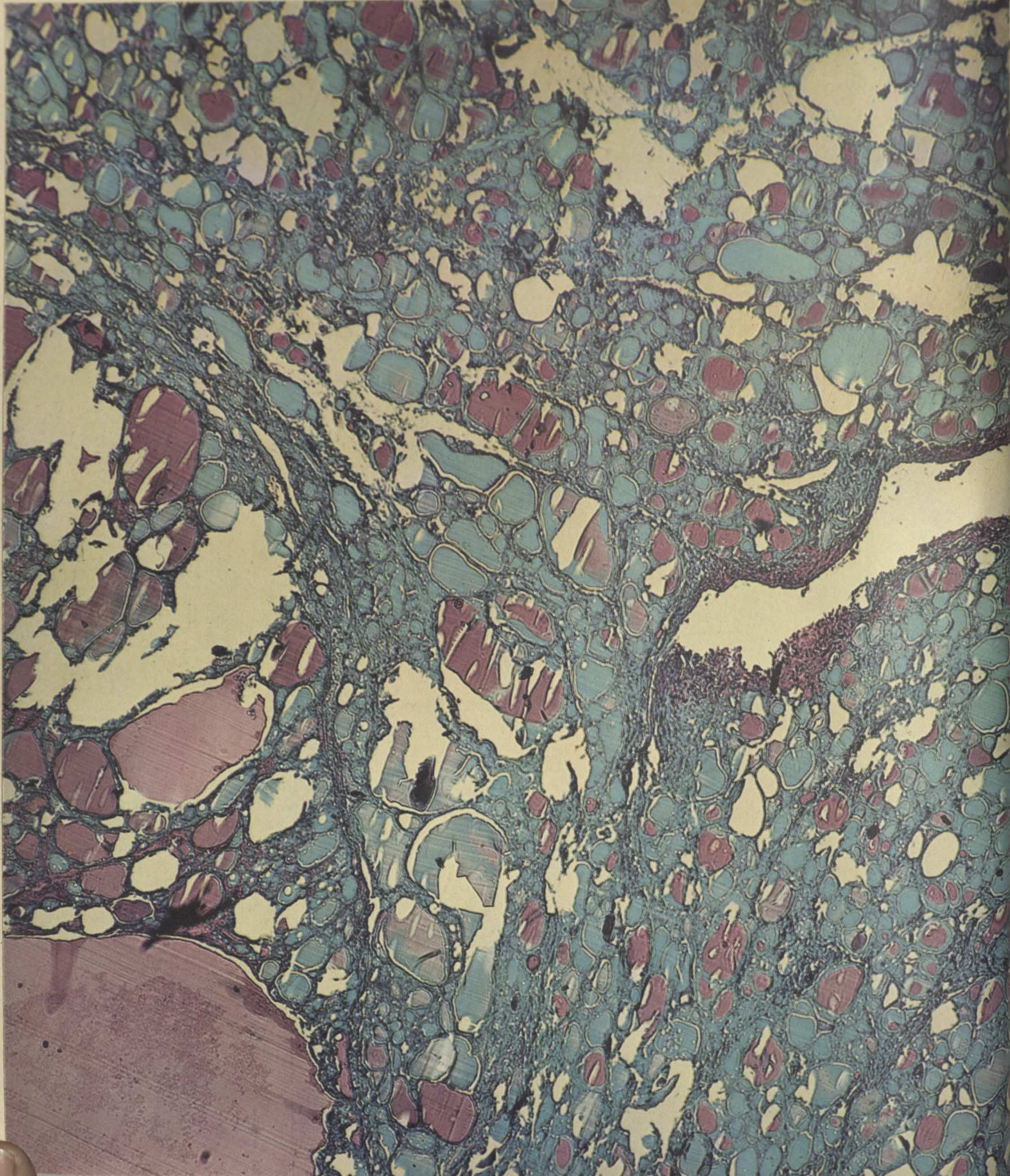
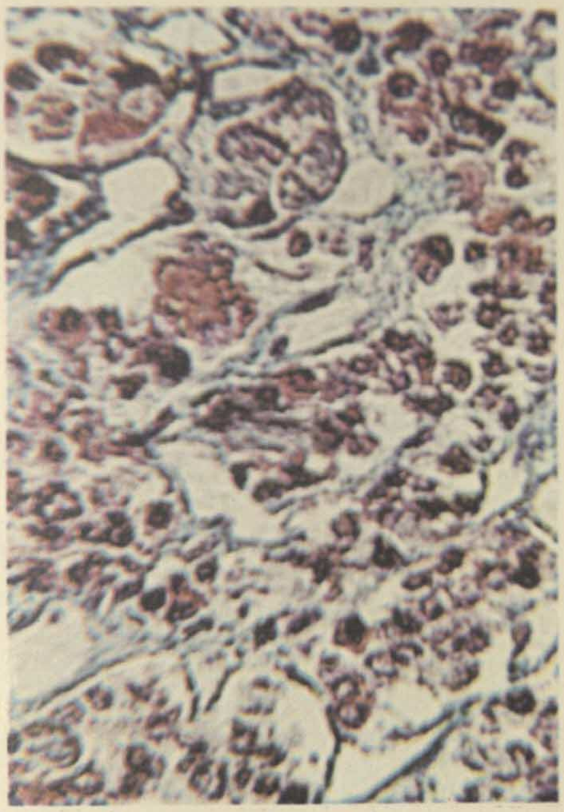
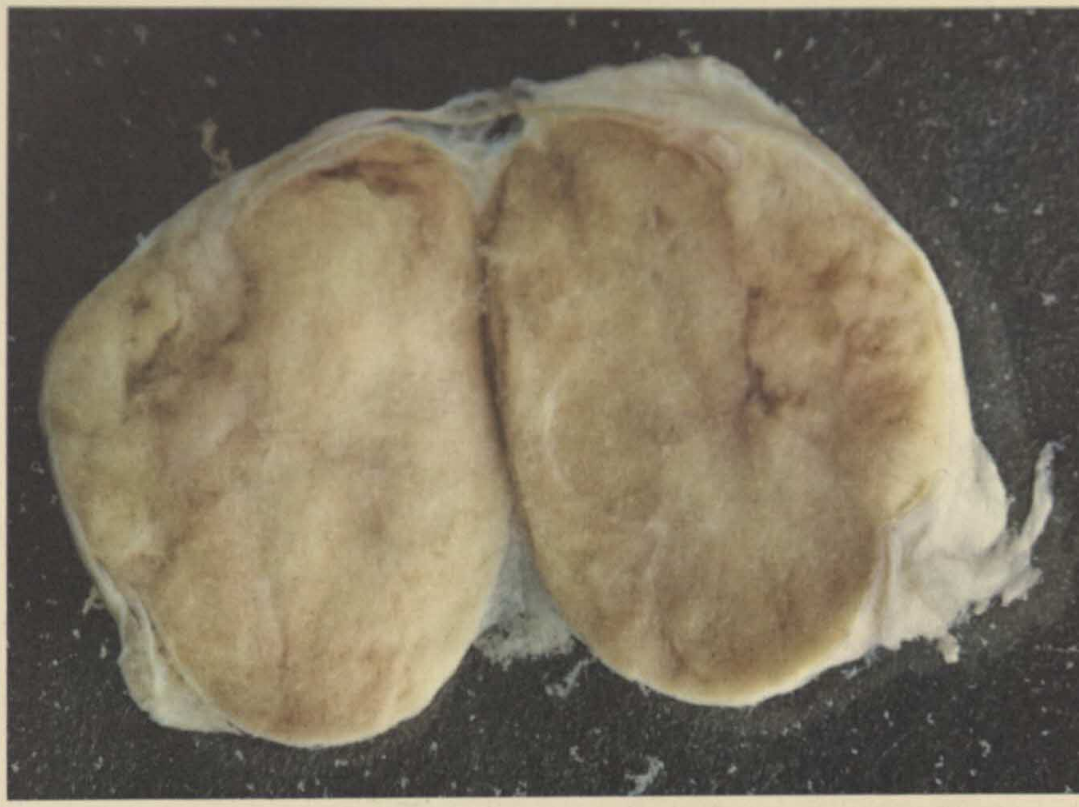


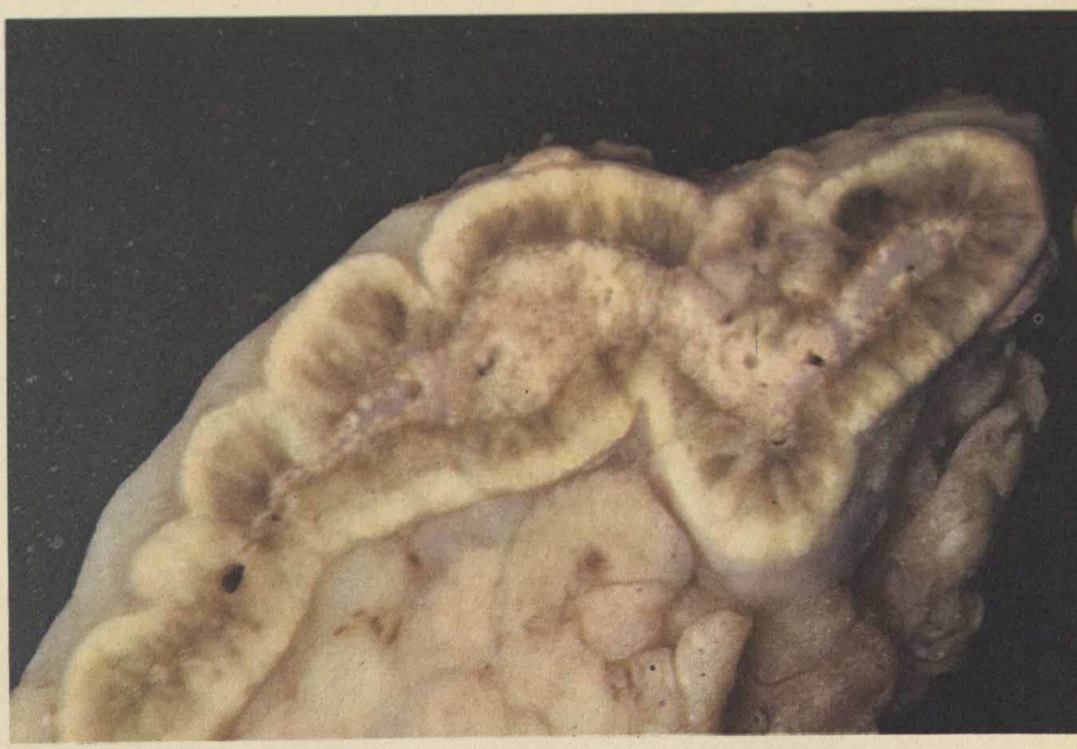
Fig. 3. Posterior view of the larynx, showing the hind surface of the thyroid gland (1) as well as the four parathyroid glands; (8) upper right parathyroid. 2 and 7, vagus nerve; 3 and 10, inferior thyroid arteries; 4, left common carotid; 5, aorta; 6, right common carotid; 9, internal jugular vein; 11, subclavian artery; 12, recurrent laryngeal nerves; 13, superior vena cava.







Three of the most important glands of internal secretion: the thyroid (left-hand page), showing the histological structure, with the vesicles that secrete colloid (mag. × 76); the pituitary, shown above on the right (actual diameter approx. 1 cm) the histological structure of which is shown in the left-hand illustration (mag. × 700); below, the suprarenal gland in two parts, the adrenal cortex forming the outer layer, the medulla forming the inner part. These parts are clearly distinguished in the photograph below on the right; the photograph on the left shows the histological structure of the gland (mag. × 50. Photo Lod).



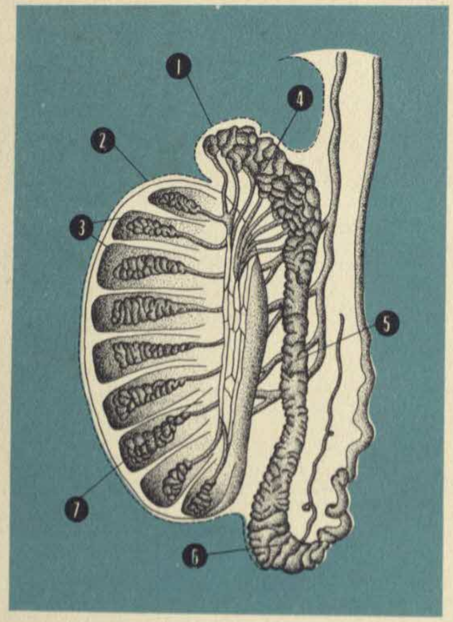


Fig. 4. Longitudinal section of a testis, the male genital gland. 1, tunica externa; 2, tunica albuginea; 3, muscle septa; 4, efferent ducts; 5, epididymis; 6, tail of epididymis; 7, seminiferous tubules in the body of the gland.

hoarse and slow and speech difficult and monotonous. Every function in the body is slowed down, sensitivity to cold is extreme and the body temperature is low. Menstrual periods disappear. Constipation is habitual, anaemia frequent and the amount of blood cholesterol is very high (two or three times normal, which is 2 to 2·3 grams per 1,000). In myxoedema patients, basal metabolism is very much lowered and thyroid fixation of radioactive iodine is greatly diminished.

In a very young child, thyroid insufficiency leads to a stoppage of growth and a retarding of bone formation. Intellectual disturbances are always present, showing themselves in a slowing down of thought and ideas. In a child, this insufficiency may lead to myxoedematous idiocy. Secondary sexual characters do not appear and genital impotence is usual.

It is easy to understand the great importance of this gland after these descriptions of excessive or deficient thyroid functioning. The gland governs these exchanges, activates most of the functions of the organism, stimulates other endocrine glands, and also stimulates (sometimes to excess) vivacity of mind and temperament.

Suprarenal glands

The activity of the suprarenal glands presents a different picture. Situated above the kidneys and of small size (weighing 4 to 10 grams), they comprise two distinct parts:

1. The medullary gland, or suprarenal medulla, connected to the nervous system and secreting adrenalin and noradrenalin, which control arterial pressure and act on the sympathetic nervous system.

2. The cortical gland (or suprarenal cortex). This is of greater importance and is activated by ACTH (pituitary corticotrophin from the anterior pituitary lobe). It secretes more than thirty hormones that have been isolated and nearly all have been synthesized. The presence of these is necessary for life. They are built up from cholesterol and are for the most part only intermediary factors in a chain of synthesis that leads to three main groups of hormones:

Aldosterone. In infinitesimal doses this controls the regulation of sodium and potassium metabolism and thus governs movements of water and salt in the body.

Cortisones (or glycocorticoid hormones). These act on the regulation of sugar metabolism, but are mainly concerned with the secretion of cortisone and its derivatives, the importance of which is known in the treatment of numerous diseases.

Androgen hormones. These represent two-thirds of the male sex hormones in man and all the male sex hormones in women.

These hormones are of such importance that the suppression of the activity of the suprarenal glands in an animal or in man leads to death in a few days. The disease which results from the slow and progressive suppression of the suprarenal glands in man (Addison's disease) is shown by extreme and increasing fatigue, loss of water and salt, lack of appetite, brown pigmentation of the skin, and digestive troubles. A person deprived of suprarenals is incapable of responding by production of cortisone substances to any shock due to trauma, infection, or poisoning, and thus he dies rapidly because he has no cortisone response.

Today, the life of a sufferer from Addison's disease can be maintained by a daily or twice-daily dose of small quantities of cortisone equivalent to those produced by healthy suprarenal glands (15 to 30 milligrams a day). Nowadays, no one dies from suprarenal insufficiency: its treatment with cortisone is certain and of mathematical efficacy.

When, on the other hand, the suprarenocortical functions are increased, stimulated perhaps by a suprarenal tumour, or more often by some abnormal excitation of the gland, due to excessive quantities of ACTH (pituitary corticotrophin), then the serious disturbance known as Cushing's syndrome occurs, as we have already mentioned. This is caused by an excess of cortisone and its derivatives, and is the same disturbance that we see in patients who are given too much or too prolonged a course of cortisone, of which we know the merits as well as the dangers. Cortisone, wonder-working hormone, cannot be administered for too long in large doses without running very serious risks. Thus the suprarenal glands, like other glands, can have excess and deficiency diseases, both equally serious and fatal. An untroubled existence cannot be enjoyed without a balanced equilibrium in the secretion of these essential glands.

Not only are they responsible for the essential mechanisms regulating water and salt content and for maintaining the equilibrium of electrolyte (sodium and potassium), but they are also the source of male hormone in the female, as well as in the male, and a source of vigour and of muscular strength and energy. They are the sources of cortisone, which has a well-known anti-inflammatory action, a powerful defence reaction against shock and a regulating effect on sugar balance.

The ease with which suprarenal hormones can be synthesized, the precision with which their concentration can be measured in the blood and the urine, and the possibility of exciting or decreasing their secretion by ACTH, have made the suprarenal endocrine glands the best known and perhaps the most important glands for the healthy maintenance of life.

The genital glands

It has long been known that testicles in men and ovaries in women have an external secretory function. In its maze of tubules, a testicle produces and matures the spermatozoa that ensure fertilization. Each month, the ovary, under the influence of pituitary hormones, ripens a follicle which reaches the surface of the gland on about the fourteenth day of the cycle and liberates the ovum. This enters the Fallopian tubes and travels towards the uterine cavity. On the way it may meet the future fertilizing spermatozoon and form the fertilized egg or sygote and then the embryo.

In addition to forming germ-cells, the genital glands contain an endocrine tissue (Leydig cells) which, under the influence of pituitary gonadotrophins, produce powerful hormones.

The testicle thus secretes *testosterone*, which is the most important of the male hormones and which, from puberty onwards ensures the development of the external genital organs, the prostate, and seminal vesicles, and affects the skin, skeleton, muscles, larynx, voice and the hair, which takes on its masculine distribution on the body with moustache and beard, and also affects the aggressiveness, character, sexual behaviour, and intellectual maturity of the male.

When male hormone is emitted in great excess, this in itself blocks the pituitary secretion of gonadotrophins, and these, by their absence, no longer stimulate testicular secretion, which is thus stopped by this system of regulation. When testicular secretion is stopped, secondary sexual characters atrophy and disappear, impotence occurs and the personality alters, losing its dynamism, aggressiveness and strength.

In the female, the internal secretion system of the genital glands is more complex. During the menstrual cycle, pituitary gonadotrophins stimulate the development of the ovum and the ovarian follicle and also the production of a very strong internal secretion from the ovary. This pours out great quantities of oestrogen, which develops the breasts and starts the preparation of the uterine mucosa. When the follicle reaches the surface of the ovary and breaks to free the ovum, the scar left by this rupture is filled by a temporary endocrine tissue, the *corpus luteum*, which secretes lutein, or progesterone, in abundance, which completes the preparation of the uterine mucosa for the reception and embedding of the sygote.

The female organism is then inundated with large quantities of oestrogen and progesterone. The excess of these hormones blocks production of gonadotrophins by the pituitary, and unless pregnancy ensues, the level of oestrogen and progesterone falls, and the uterine mucosa, no longer supported by these hormones, is reduced by haemorrhage. This is the menstrual cycle, which is then repeated.

The existence of this hormonal cycle is the most perfect example of the combined actions of glandular secretions and the interrelation of pituitary and ovary.

An infinite variety of disturbances may be caused by an insufficiency or an excess of hormonal secretions, or by disturbances of the diencephalon and pituitary that control them.

There are few fields of hormone action where the diencephalon, which reflects physical and psychological activities, does not act directly on the glands. Everywhere we see the preponderating action of this diencephalic centre on the activity of the endocrine system and the glands of internal secretion. This essential concept must dominate any account of hormonal secretions, and emphasizes the importance of the control that the brain exerts on the endocrine system. It is by means of this concept that the close relationships may be explained between physical, psychological and moral activities, between instinctive preoccupations or repressions, affective disorders, disturbed family situations, as well as the whole life of the glands of internal secretion and their hormones. These, in turn, react strongly on psychological, affective and emotional life, of which they are the activators and regulators.

Even in this short outline, the extreme importance and complexity of the function of the endocrine glands and their hormone secretions will be clearly apparent. The study of these glands constitutes one of the most important and best known chapters of modern physiology and medicine. We live and act by our hormones, which control our vitality, our character, our equilibrium, our instincts, our wishes and dreams and animate our lives.

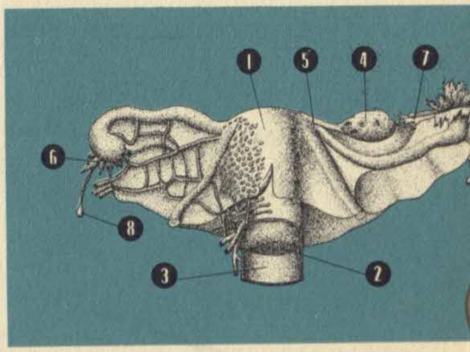
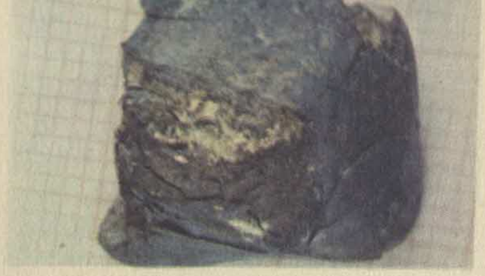
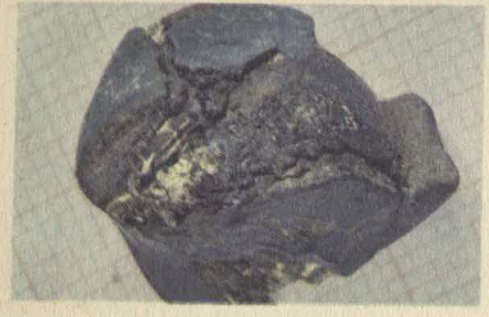
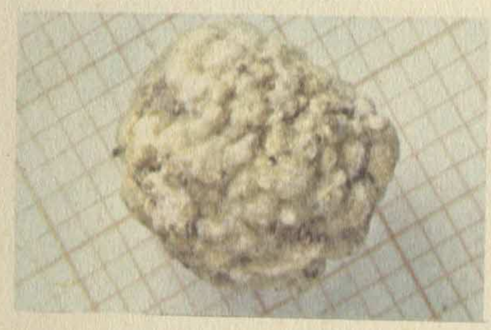
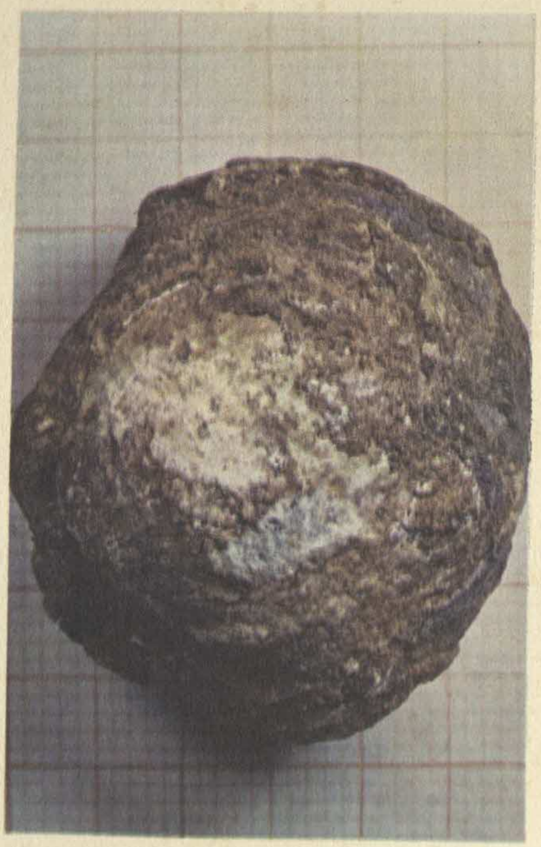


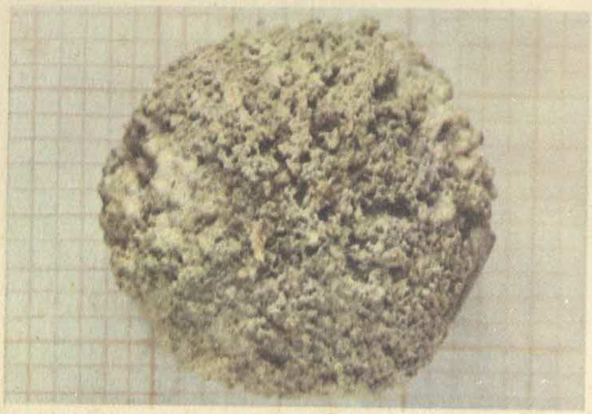
Fig. 5. General view of female genital apparatus; (4) ovary, a gland of internal secretion; 1, body of the uterus, covered by the peritoneum; 2, neck of the uterus; 3, vagina (cut open); 5, ligament connecting ovary to uterus; 6, uterine horn: left, *in place,* right, *showing infundibulum; 7, ovarian fimbria of infundibulum; 8, hydatid of Morgagni* (left).

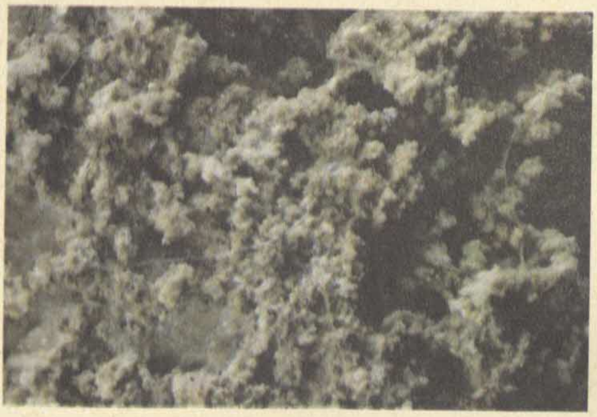






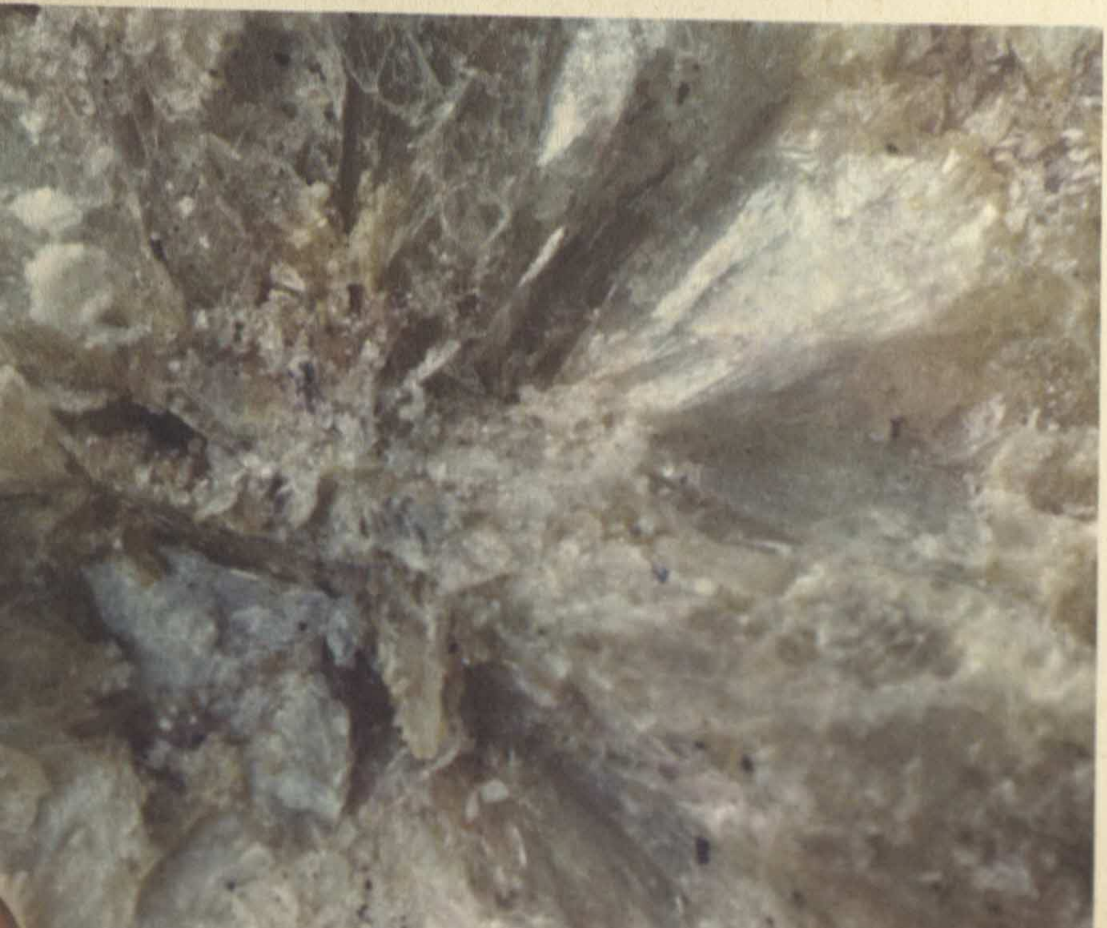


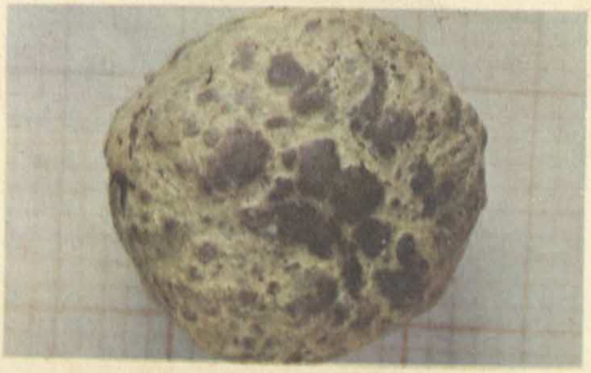


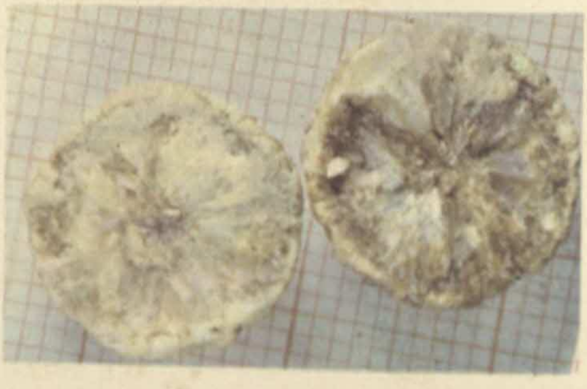


Biliary calculi

Among the disorders caused by defective functioning of the digestive system, one of the best known is the formation of biliary calculi. These illustrations show a few impressive examples. Following metabolic disorder, pigments or cholesterol contained in bile form concretions or 'stones' which are often very painful and can only be removed by surgery. (Photos Lod).







Diabetes

Ronald E. TUNBRIDGE

Diabetes mellitus is a syndrome characterized by hyperglycaemia and glycosuria in which there is an impairment of the body's power to utilize glucose efficiently. The disorder is widely prevalent in the human race and also occurs in a number of other animals, notably dogs.

Excellent descriptions of the disease are to be found in early Indian and Chinese writings. In England, Willis (1621–1675) was the first person to suggest that the urine contained sugar, a fact later confirmed by Dobson in 1766, but it was left to von Mering and Minkowski, in 1888, to demonstrate experimentally that the removal of the pancreas in dogs led to the development of diabetes mellitus.

Langerhans was the first to describe the islets in the pancreas. The pancreas has two main groups of cells, the acinar cells surrounding the small ducts which unite to form the pancreatic duct and convey the enzymes essential for the digestion of food; and a small group of cells, the islets, with a rich blood supply and a nerve supply from the vagus. Diamare, in 1899, described two kinds of cells in the islets, now referred to as the alpha and the beta cells. Several workers suspected and suggested that the islet cells might manufacture a hormone, the absence of which might lead to the development of diabetes mellitus, but such theories were not substantiated until Banting and Best, in 1921, demonstrated that the hormone, insulin[1], was derived from the beta cells. Later work has provided evidence that another hormone, glucagon, is derived from the alpha cells.

Diabetes mellitus may be produced in animals by a variety of procedures: (1) removal of the pancreas; (2) injection of anterior pituitary extract; (3) administration of alloxan; (4) over-production or the administration of large quantities of steroids; and (5) perfusion with large quantities of glucose.

(1) The original experiments of Mering and Minkowski consisted in the removal of the pancreas. In many animals the removal of nine-elevenths of the pancreas does not necessarily lead to the immediate development of diabetes mellitus, but it is very liable to produce it later. This experimental procedure has been used to determine the factors which might aggravate a tendency to diabetes, particularly the effects of different diets. Experiments have been made where a small portion of the tail of the pancreas has been transplanted to the neck and the remainder of

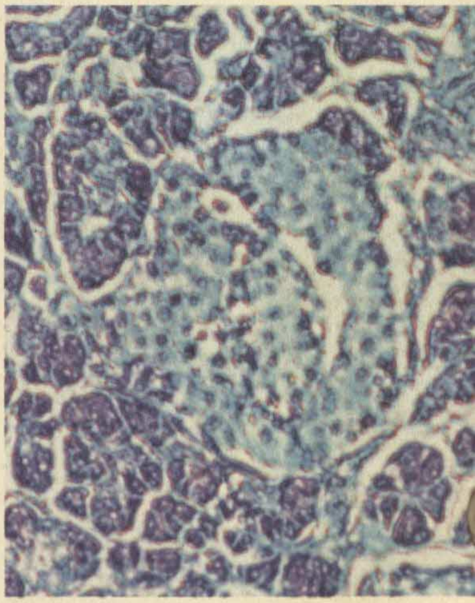


Fig. 1. Microphotograph of an islet of Langerhans, the endocrine section of the pancreas. (Photo Lod).

(1) *Insulin is a crystalline protein having a double chain of 51 amino acids and 2 bisulphide links. It is not yet known precisely how it acts.*

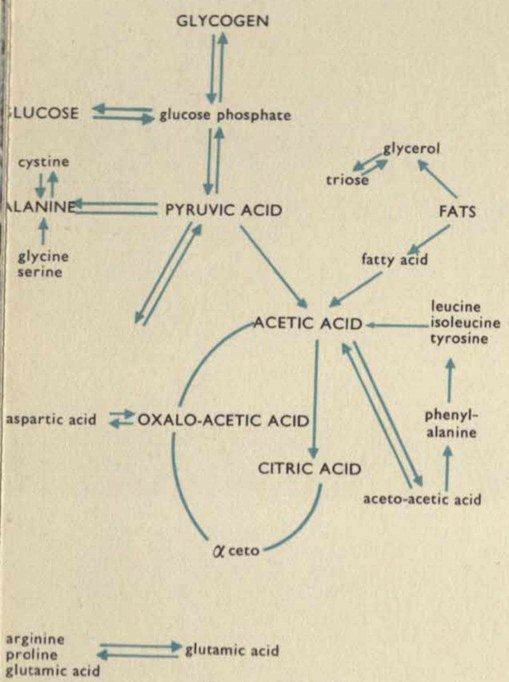


Fig. 2. Simplified diagram of Krebs' cycle, the best-known and most important of all metabolic reactions, where sugars and fats are converted by the cells into energy. This process is strongly affected by certain malfunctions, one of the most serious being diabetes.

the pancreas removed. In cases where the animal recovered but did not develop diabetes and the transplanted portion of the tail was later removed, severe diabetes developed immediately.

(2) Young (1937) was the first person to produce diabetes mellitus by the injection of anterior pituitary extracts. It was found that injections had to continue for some time if permanent diabetes was to develop. Moreover, the development was associated with a series of changes in the beta cells of the islets of Langerhans, which suggested that the effect of the injections was initially to cause the overproduction of insulin, followed by exhaustion and ultimately atrophy of the beta cells. The injection does not produce diabetes with equal regularity in all animals, and even within one species susceptibility varies.

(3) Alloxan was initially used experimentally in animals because of its toxic effect upon the renal tissue and it was only by chance that it was found to have an equally toxic effect upon the beta cells of the islets of Langerhans. Its effect and its individual action resemble that of anterior pituitary extracts in several respects.

(4) The administration of large doses of steroids both to animals and to human beings has been observed to be followed by the development of hyperglycaemia and glycosuria. In most instances, however, the resultant symptoms are mild, but when therapy is stopped it has been noticed that abnormality may persist.

(5) Lukens and Dohan (1948) were able to produce diabetes mellitus in cats and in dogs following either the intraperitoneal or the intravenous infusion of massive quantities of glucose. Again there was great variability in response.

Natural insulin

Insulin was isolated as a comparatively pure protein by Abel in 1926, and Scott demonstrated the need for the presence of zinc in order to obtain insulin crystals. The use of counter-current distribution by Harfenist and Craig (1952) revealed the presence of two major and two minor components in insulin, and Sanger and his colleagues (1954) found that it contained 51 amino acids.

The precise mode of action of insulin is still not certain, but we know it plays an important part in the regulation of blood sugar, its deposition, conversion and circulation and that its effect is not confined purely to carbohydrate metabolism.

Regulation of blood sugar

The regulation of the blood-sugar level is subject to the control of many influences other than insulin, such as the rate of absorption from the alimentary canal, which can be affected by liver disease. The influence of the nervous system through the vagus nerve and the sympathetic control of the adrenal glands must also be considered, as must the secretion of the pituitary gland. If damage to this gland, from atrophy or removal of its anterior lobe, is followed by a small dose of insulin, severe hypoglycaemia occurs. The suprarenal gland is also thought to have an anti-insulin effect; eg, certain cases of Cushing's syndrome, a disorder associated with hyperplasia of the adrenal cortex, develop glycosuria.

The incidence of diabetes mellitus in the human is on the increase, largely because of the ageing composition of the communities of Western Europe and North America. Nearly fifty per cent of all the cases of diabetes mellitus have their onset between the ages of forty to sixty. A series of community surveys in North America, Wales and England, have revealed a total incidence, including both the known and the latent cases, of 1·0 to 1·4 per cent.

Prior to the age of forty there is little difference in the sex ratio, but thereafter the disorder is found more frequently in women.[2]

Symptoms

The symptoms of diabetes in the severe cases are striking; they are thirst, polyuria, extreme loss of weight, emaciation and general debility, coupled with a susceptibility to develop infection and ultimately the development of ketosis, coma and death. In many persons the first indication of the possibility of diabetes mellitus is the finding of glycosuria at a routine or special medical examination.

Aetiology in humans

Although Banting and Best clearly proved that insulin was formed from the pancreas and that the administration of insulin would reverse all the acute symptoms of diabetes mellitus, certain clinical and pathological observations have made it difficult to accept the hypothesis that diabetes arises purely as a result of an absolute deficiency of insulin. Indeed, its true aetiology is unknown.

Trauma, infection, and stress have not been shown to be causal agents, although any one of them may aggravate the condition once

[2] *A study by Pyke (1959), confirmed by Malins (1961), suggests that repeated pregnancies may have something to do with this phenomenon.*

[3] *It is now considered that daily calorie requirements are 2,600–2,800 calories for men and 2,100–2,400 calories for women. Before the Second World War it was considered to be 3,300 for men and 3,000 for women.*

[4] *A survey has given the following figures: 17 per cent of patients followed their regime satisfactorily and did not discard more than 10 per cent of their diet, 47 per cent were average (less than 20 per cent) and 36 per cent were not satisfactory.*

it is established. The only known aetiological factor in human diabetes is an inherited tendency to the development of the disorder.

Treatment

In the absence of insulin the body can metabolize carbohydrate, but the reaction is slow and the tissues in general are unable to deal with a sufficient quantity of glucose to provide the energy necessary for normal existence. Thus the foundation of the treatment of diabetes lies in reducing the metabolic load with which the body has to deal. Many dietetic regimes have been tried for the treatment of diabetes mellitus, but there is widespread agreement today that calorie restriction is the most important single factor in treatment.[3]

In deciding on the dietetic requirements for diabetic patients, it is necessary to take into account not only their work but also their general mode of life, their age, their sex, their general constitution and build, and whether they were over- or under-weight before the onset of the diabetes. It is well to remember, even then, that dietary control is very difficult to achieve, and that rigid diets without 'free' selections are neither good nor necessary.[4]

Today 50 per cent of the known diabetics in a community should be satisfactorily controlled by diet alone and only for the remaining 50 per cent will it be necessary to prescribe insulin or a hypoglycaemic agent.

Insulin

Despite the lack of ability to classify accurately the true nature of the disorder in diabetes mellitus, dietary control and insulin therapy have enabled diabetic subjects to lead full, active and relatively normal lives for their age and state of general health.

The individual requirements for insulin vary from patient to patient.[5] It is customary to use soluble insulin for emergencies or for the treatment of diabetic coma. The aim of treatment is to maintain the blood-sugar level within as nearly normal limits as possible and below 200 mg per cent at all times during the twenty-four hours of the day.

Despite the availability of so many insulin preparations, an endless search has been maintained to find a preparation which can be taken orally.

By means of diet, together with insulin or the use of hypoglycaemic agents, diabetes mellitus can be controlled, but the therapy does not provide a complete substitution, as is the case with the use of 1-thyroxine in the treatment of myxoedema—thyroid deficiency.

Individuals suffering from diabetes mellitus are prone to develop vascular lesions in the retina, lesions affecting the kidney, and also lesions of the nervous system. There is considerable pathological evidence to suggest that these complications are specific to diabetes mellitus, since similar lesions are rarely found in other disorders. It is these complications which provide the problems and the anxiety about the treatment of diabetes mellitus today. Experimental animals have not proved helpful in resolving these problems since many of them do not suffer from these disorders. Clinical experience would suggest that careful control does reduce the incidence of their severity but that it is not a guarantee against their occurrence.

(5) *A check on daily fluctuations of blood glucose are required before prescribing an insulin dose. A single daily dose of lente-insulin, zinc-protamine insulin or isophane insulin is sufficient for most diabetics. If a patient should need more than 60-80 units per day, a single dose may not suffice.*

HISTORICAL NOTES

Seventeenth century

WILLIS (1621-1675) advanced the hypothesis that sugar is present in urine.

1766

DOBSON confirmed Willis's hypothesis.

1888

VON MERING and MINKOWSKI demonstrated that removal of the pancreas in dogs leads to diabetic symptoms.

1921

BANTING and BEST showed that the beta cells of the islet of Langerhans manufacture a hormone (insulin). Later it was observed that the alpha cells produce a different hormone (glycogen).

1937

YOUNG succeeded in producing experimental diabetes with injections of pituitary extract, obtaining an alteration of the beta cells, with overproduction of insulin followed by the death of the cells. Results vary from one species to another, even from one animal to another. Generally, massive doses of steroids cause hypoglycaemia and glycosuria in man as well as in animals.

1948

LUKENS and DOHAN produced diabetes in cats and dogs with intravenous perfusion of massive doses of glucose.

Man and malnutrition

J. F. BROCK

Digestion and assimilation of food

The physiology of appetite is still obscure. There is undoubtedly a part of the brain to which damage can cause appetite perversions. The exaggerated movements of an empty stomach and too low a level of sugar in the blood (hypoglycaemia) stimulate appetite as do the odours and memories of good food. All of these organic factors are overlayed and built into a complicated system by mental processes.

The relations of the infant with its mother in the first few years of its life may determine unconscious and subconscious attitudes to food which have important repercussions in later life. Nagging by the mother during mealtimes may lead in the young child to resistance through which, in the end, the mother is delivered into bondage to the whims and caprices of her child. A more serious result may be the formulation of neurotic symbolism which leads to eventual refusal to eat sufficient for health (anorexia nervosa). Such obsessions may develop in adolescence or early maturity as a result of unhappy love affairs or may result from definite mental illness (psychosis).

In another direction unhappiness and neurotic attitudes may lead to compulsive or obsessional eating and be one of the contributary causes of obesity.

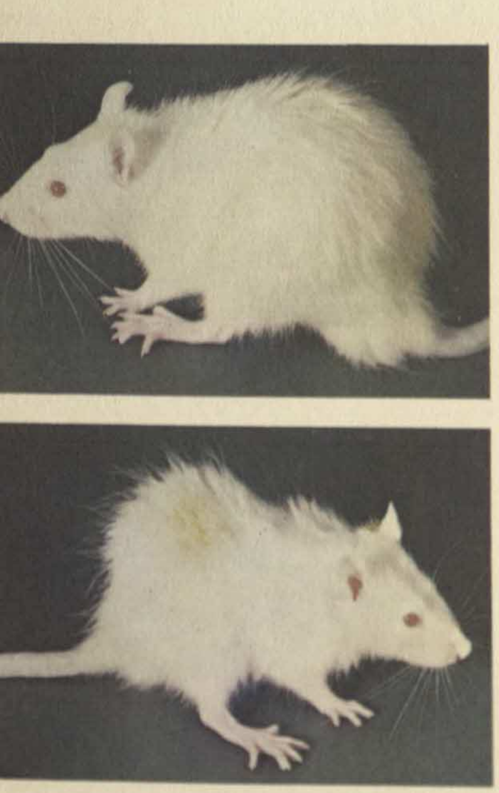


Fig. 1. Male rats fed on an adequate diet for five months without, however, any vitamins. The rat in the top photograph has received an additional 1 cc of orange juice per day.

Foods and nutrients

From the point of view of nutrition, the body can be likened to a hollow tube in which the gastro-intestinal tract from the mouth to the anus represents the lumen of the tube—while the body tissues which have to be nourished represent the thick walls of the tube. Food enters the lumen of the tube at the mouth and is digested in the mouth, stomach and upper small intestine. Throughout the small intestine the products of digestion have to be assimilated or absorbed by intricate vital mechanisms dependent upon a multitude of enzymes. In the large intestine or colon some water is absorbed, some excretion takes place and under the influence of the normal bacteria, cellulose is digested and some vitamins are synthesized. Finally, the useless residue of the food is excreted at the anus. Ordinarily these processes are very efficiently carried out even when there is indigestion and constipation. Severe or prolonged diarrhoea may interfere considerably with digestion and absorption but it is surprising how much of the nutrients derived from food are assimilated even in the face of considerable diarrhoea.

There is a group of disturbances called malabsorption syndromes with or without steatorrhoea (the presence of recognizable excess of fat in the stools) in which for inherited or acquired reasons the processes of assimilation or absorption are impaired. In such cases the incompletely assimilated food is attacked by bacteria in the colon, with the production of flatulent discomfort and malodorous stools. Ordinarily, man lives in symbiosis with the bacteria in his colon. They flourish on some of his intestinal secretions and the residue of his food while benefiting him by providing him with vitamins and protecting the intestinal tract against invasion by harmful bacteria.

After nutrients have been absorbed or assimilated they have to go through a great variety of metabolic processes before they are incorporated for the growth and maintenance of healthy tissue. Disturbance of these processes may lead to malnutrition even when a perfect diet is being eaten.

In his 'History of Nutrition' McCollum has traced the fantastic advances of nutritional science in the first forty years of the twentieth century. By 1940 some forty indispensable nutrients had been identified. These include essential amino and fatty acids, vitamins and mineral elements, some of the latter necessary in considerable quantities, others only as trace elements. (Oxygen and water are strictly speaking essential nutrients, although they are not ordinarily referred to by that name.) Foods therefore consist of mixtures of nutrients, usually classed according to the important contribution they make to nutrient requirement. For example, *staple foodstuffs* are those upon which we chiefly rely for the supply of energy to the body. *Protective foodstuffs* are those which contain important essential nutrients such as amino acids, vitamins and trace elements.

The important *energy-yielding foods* are classed as *carbohydrates*, *fats* and *proteins*. Practically all foods contain some protein and most so-called protein-rich foodstuffs contain both carbohydrate and fat. Protein-rich foodstuffs are quantitatively rich in nitrogen, an essential component of amino acids, but are also qualitatively rich in the essential amino acids which the human body cannot synthesize for itself. In addition, protein-rich foodstuffs usually contain some fat and carbohydrate and important essential vitamins and trace elements. For these reasons a diet cannot be healthy unless it contains a certain percentage of protein-rich foods, usually expressed as nitrogen.

Protein malnutrition

Throughout the world this percentage tends to be about 10 to 13. In under-privileged countries if the percentage falls lower than this there tends to be some failure of appetite and calorie intakes are voluntarily restricted. If the diet does not improve and energy expenditure cannot be reduced the result is *protein malnutrition,* especially when the staple foodstuff consists of carbohydrate-rich, protein-poor foods such as roots and cereals.

When growth is occurring rapidly more protein is required than in the case of the adult, who requires it mainly for tissue repair. Growth rate in infancy is especially dependent upon it. The infant at the maternal breast is consuming a well-balanced diet and his growth rate will be dependent upon the quantity of milk consumed. Bottle-fed infants may grow faster than breast-fed infants because the quantity of milk consumed and its calorie value per unit volume may be greater.

Throughout a large part of the world infants are weaned from the maternal breast on to diets which are largely or wholly starchy, such as paps prepared from cereals and roots. In many parts of the world almost every infant is affected to a greater or lesser extent by protein malnutrition. In an extreme form this leads to the disease known in Africa as kwashiorkor (figs 1–4) and to related diseases in other parts of the world. For the average child malnutrition is slowly corrected as the growth of teeth and strength enables it to compete more effectively for the limited quantities of protein in the family pot. During the same period the slowing of growth is slowly reducing the required ratio of protein to calories.

In certain communities the calorie yield from protein foodstuffs is probably much higher. There is at present interest in the possible injurious effects of excessive protein in the diet. In heavily populated regions it can at least be said that the provision of more than 10 to 13 per cent of calories from protein foods is economically wasteful.

Energy foods

The balance of calories is probably best obtained from a mixture of carbohydrates and fats. Fats have the advantage of making diets palatable and being a concentrated source of calories (9 calories per gram). If the fats are not judiciously mixed with carbohydrates (4 calories per gram) many people become bilious. The present tendency is to recommend that somewhere about 30 per cent of calories be derived from fats. This leaves some 55–60 per cent of calories to be derived from carbohydrates.

Protective foods

Deficiency of a single non-calory or protective nutrient may produce serious disease even if the diet is otherwise adequate. For example, scurvy results from a deficiency of vitamin C and beri-beri of vitamin B_1 (thiamine). These single-nutrient diseases can be produced experimentally in man, but seldom occur in nature because deficiency of one nutrient in mixed foodstuffs is almost invariably associated with deficiency of several others, especially vitamins.

Conditioned malnutrition

Malnutrition can result from a great variety of disturbances of digestion, assimilation and metabolism. Thus in almost every disease of any severity and duration malnutrition becomes evident. Appetite tends to fail, digestion and assimilation may be impaired and many of the processes of metabolism are disturbed. Such types of malnutrition are referred to as malabsorption syndromes. They are best known in the form of sprue (fatty diarrhoea, steatorrhoea).

The effects of malnutrition

Incipient malnutrition, whether dietary or conditioned, shows itself in loss of weight, vigour and vitality. If it continues, signs appear in the mucous membranes (lips, mouth and tongue) and the skin, the hair and finger nails. Thus in chronic iron deficiency the finger nails become brittle and lose their lustre and eventually their convex surfaces become concave (koilonychia).

Other forms of human malnutrition present fairly well-defined clinical syndromes, such as swollen spongy gums and bleeding into the muscles in cases of scurvy, the sym-

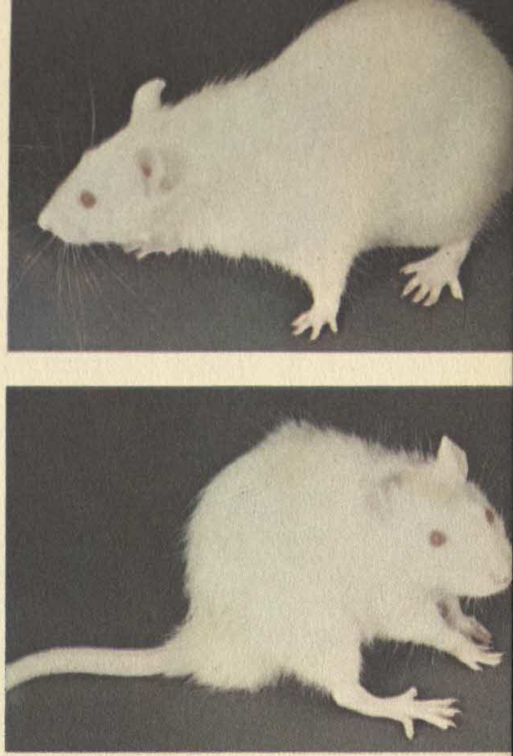


Fig. 2. Below: the rat from the top of fig. 1. Above: an animal of the same age on the same diet with a supplement of all vitamins.

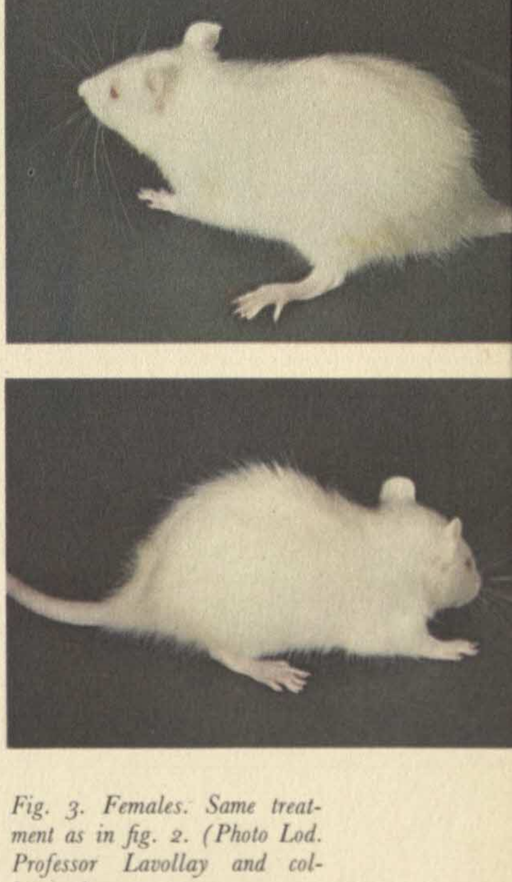


Fig. 3. Females. Same treatment as in fig. 2. (Photo Lod. Professor Lavollay and colleagues).

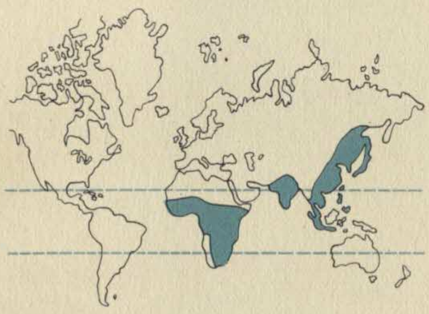


Fig. 4. World distribution of primary liver cancer (from C. Berman, 1952). The tropics are shown by the dotted lines.

metrical light-sensitive skin eruption of pellagra and the disturbance of heart and circulation in beri-beri (thiamine deficiency). But it is unusual to encounter in man pure deficiencies of a single nutrient; the clinical pictures of malnutrition are variable and often mixed.

Subnutrition

Before any signs are recognizable by the doctor it may be shown by biochemical study that the body has insufficient reserves of one nutrient or another, or shows biochemical disturbances of metabolism, such as increased excretion of xanthurenic acid in the urine of incipient cases of pellagra. Even before these biochemical disturbances can be identified it is probable that impaired health and vitality result from minor degrees of malnutrition. This type of borderline malnutrition is called sub-clinical nutrition or subnutrition. In children it is sometimes possible to demonstrate better growth or a lower prevalence of infection in large groups under the influence of good feeding. But it is seldom possible to make such a demonstration on the individual child or even on groups of adults.

Malnutrition

During the last two decades there has been an increasing awareness of the possibility that man's constitution, and therefore his liability to infective, degenerative and other types of disease, may be determined by his diet. Primitive mythology is full of allusions to the possible effects of various foodstuffs on physique, longevity and even temperamental characteristics such as bravery and cowardice. Several decades ago attention was drawn by Orr and Gilks to the remarkable differences in physique, experience of illness and temperamental characters between the adjacent Masai and Kikuyu tribes of East Africa. The former, who are largely carnivorous, extolled the virtues of a mixture of blood and milk as the diet for their young warriors. The Kikuyu, on the other hand, are predominantly vegetarians. McCarrison made similar observations in India and tried the effects of different human diets on laboratory rats. At the International Nutrition Congress at Amsterdam in 1954, several papers were presented on the physique and health of vegans. The latter are people who, for religious or other reasons, eschew not only the flesh of animals, poultry and fish, but even animal products such as milk, cheese and eggs. It is generally accepted that man can live indefinitely in perfect health on a vegetarian diet which excludes milk, cheese and eggs. Sufficient quantities of expensive high-protein vegetables, such as nuts, must, however, be included in the diet to render it fully balanced.

Since the Second World War great attention has been paid to geographical pathology, particularly to the possible role of diet in determining constitution and disease-susceptibility. Two important problems have been intensively studied: (1) the possible role of protein malnutrition in determining susceptibility to early cirrhosis and primary cancer of the liver in underprivileged populations, and (2) the possible role of excessive fat, particularly of animal origin, in determining premature atherosclerosis and its complication, coronary heart disease, in privileged groups.

A very important series of reports by Dubos and his colleagues at the Rockefeller Institute lays a new basis for the understanding of a previously puzzling contradiction of evidence on the relation of diet to infection. These reports show that 'the diets most effective in assuring rapid growth of non-infected animals are not necessarily the ones that give the greatest resistance to infection. In other words, the ability to confer resistance is a criterion different from those usually considered by nutritionists'.

Endemic cirrhosis and primary cancer of the liver

Throughout a large part of the African continent and in other tropical regions (excluding Central America) there is a high prevalence of primary cancer of the liver in young adults, particularly males. This almost invariably develops as a result of cirrhosis, the first evidence of which is often to be found about the age of twenty. It appears to have little if any connection with alcohol. At first it was thought that parasites and other factors peculiar to tropical climates might be responsible. Careful geographical studies have shown, however, that the same cirrhosis with its attendant primary cancer is encountered among underprivileged people in regions outside the tropical belt and free from tropical parasites. The same studies have shown close geographical correspondence between this group of liver diseases and the post-weaning syndrome, kwashiorkor, which is the result of protein malnutrition. It is therefore reasonable to conclude that protein malnutrition may have been an original contributory cause.

Dietary fat and coronary heart disease

After the Second World War reports appeared from the Scandinavian countries showing a sharp fall, during the early years of the war, in the mortality from coronary heart disease and a steady rise to pre-war mortality in the few years succeeding the war. This form of heart disease is becoming an increasingly important cause of sudden death or disability in middle-aged males. Its proximate cause is a narrowing of the lumen of the coronary arteries which nourish the perpetually active muscle of the heart. This narrowing is due to deposit under the endothelium of the artery of a porridge-like substance called atheroma. Atheroma of the coronary arteries may, however, be moderately marked for a long period of time without any serious effects. If, however, the remaining narrowed lumen is suddenly obliterated by thrombosis of the blood at that point, the heart muscle seizes up.

Epidemiologic studies by Keys and his colleagues have shown that the increasing prevalence of coronary heart disease is statistically associated with economic privilege, a constant feature of which is the presence of larger quantities of fat in the diet, particularly fat of animal origin (saturated fats). Another close correspondence was with the level of total serum cholesterol in the blood serum. Saturated fats raise the level of serum cholesterol in man; unsaturated fats (of vegetable or marine origin) reduce its level. All diseases in which the serum total cholesterol is raised show an increased prevalence of coronary heart disease.

Part of the answer, therefore, to the increasing prevalence of coronary heart disease, would be to reduce the total fat consumption in the diet and to substitute approximately half of the saturated fats by unsaturated fats of vegetable or marine origin.

Obesity

Great efforts have been devoted to elucidating the various types of obesity but the cause of the commonest remains something of a mystery. Exogenous obesity can be attributed to the habitual consumption of calories far in excess of the average requirements. Endocrine obesity can be attributed to identified disturbances of the endocrine glands. Other uncommon examples may be due to disease of, or damage to, the area of the brain known as the hypothalamus, which regulates the concerted action of the endocrine glands. Most cases cannot, however, be defined in these terms, but rather as constitutional obesity, in that there is both an inherited factor and an environmental complex, the latter acting on the former over a considerable period of time. The essence of this environmental complex is the consumption, not of more calories than the average person, but of more calories than the metabolism of the body can dispose of. Many people, probably the majority, are able habitually to consume more calories than they need and to dispose of the excess by dissipation of heat. The unfortunate minority are liable to constitutional obesity because they cannot dissipate excessive calories but tend, rather, to lay them down as subcutaneous fat. In such people the habitual consumption of even fifty calories in excess of daily requirements will lead to obesity. They can always correct this by reducing their calorie intake to less than their requirements and at the same time eating all the necessary nutrients for healthy growth and maintenance. Unfortunately, such people often possess a temperament which undermines their attempts to deny themselves.

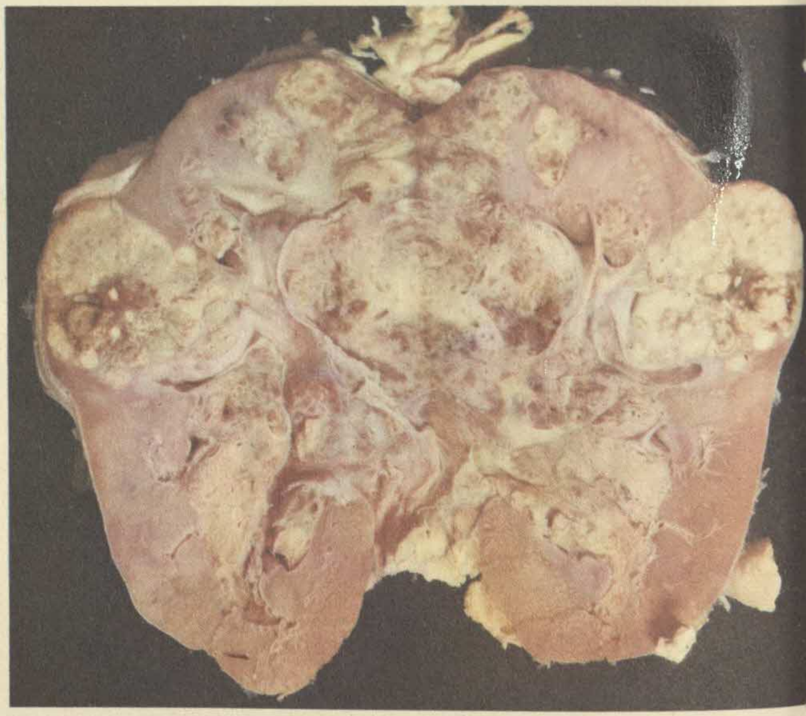
World population, growth and food supplies

The numbers of over-nourished people in the world is only a fraction of the number of malnourished. Nor is it solely a problem of ignorance, superstition and traditional holding of old ideas on cooking and eating. The production of protein-rich foodstuffs, if not of calories, is grossly deficient in relation to the world's population. This leads to widespread deficiency of amino acids and certain vitamins ordinarily supplied by protein-rich foods (eg vitamin B_{12}). The same shortage of protein-rich foodstuffs probably contributes to widespread deficiency of mineral (including trace) elements.

The Director of the Nutrition Division of FAO has estimated that

> 'the yield of food from the present cultivated part of the world's land surface could be increased by 50–100 per cent by better methods of agriculture, fertilization and pest control; and . . . the present arable area of the earth's land surface . . . by perhaps 100 per cent. We must conclude, therefore, that an increase in both quantity and quality of foodstuffs proportionate to present rates of world population increase are not technologically impossible'.

PART THREE



The most serious disorders, especially those of which the origin cannot be determined and which cannot be adequately treated, are found in the cells and tissues. Most frequently attacked are the connective tissues (especially bones and joints); here disorders lead to arthroses and rheumatism, suffered by a large number of people. Of even greater

Tissue and cell disorders

concern is the cell disorder known as cancer which, as an anarchic proliferation of cells, may affect any part of the body. One of the most destructive forms of cancer is leukaemia, which affects the blood cells. The illustrations show, from top to bottom and from left to right, a secondary liver cancer, a primitive renal cancer, a secondary lung cancer and metastatic cancerous cells (mag. × 3,000). Note on the photographs of secondary cancer the white nodules that show the spread of cancerous cells (metastasis). (Photos Lod, the photograph on the right was taken at the Departmental Blood Transfusion Centre of the Seine).

Bones and joints

André PELTIER

Of all organic disorders, rheumatic disturbances are the most frequent, the most difficult to understand, and the most difficult to treat. Despite a great deal of research, very little is yet known about their mechanisms. They are difficult even to define and their terminology is not precise. The same words have different meanings in different countries. Yet although we are dealing here with a social scourge which cripples millions of people and which has been the subject of much research throughout the world, our knowledge of this form of disease is still beset by uncertainties.

(1) *Arthritis: 'Chronic diseases of joints, the anatomical lesions of which consist mainly of destructive changes of articular cartilage or fibro-cartilage, associated with proliferative lesions of underlying osseus tissue; the synovial membrane shows only intermittent or secondary chronic inflammation.' (From Sèze.) This includes most conditions of the kind commonly referred to as 'rheumatism'.*

The importance of the morbidity of rheumatic diseases is shown in the statistics given on the left, showing the figures for the United States in 1938; generally speaking, this picture remains valid.

Diseases	*Number of cases*
Rheumatism	6,850,000
Cardiac diseases	3,700,000
Hypertension	3,700,000
Varicose diseases	1,750,000
Kidney diseases	1,550,000
Nervous diseases	1,450,000
Cancers and tumours	930,000
Tuberculosis	680,000
Diabetes mellitus	660,000
Gastric ulcers	330,000

These diseases top the frequency charts of chronic illnesses; every year they incapacitate ten times more people than do diabetes and tuberculosis, seven times more than cancer, and twice as many as heart disease; it is a social plague that causes many individual tragedies and certainly justifies the extensive research carried out on rheumatic diseases.

Such research opens up many possibilities because the term rheumatic disease embraces a large number of very different and varied illnesses. There is considerable disparity in their importance, but rheumatoid arthritis and degenerative arthritis preponderate. Nevertheless, despite the great variety of these diseases, they all have one anatomical feature in common—the tissues in which these diseases become manifest. Rheumatism is a disease of supporting, or connective, tissue. The study of this tissue and its histological and biochemical deterioration provides the best means of elucidating the mysterious nature of these diseases.

In most organs, connective tissue has only a limited quantitative importance; it forms an intercellular system, giving the cells physical support, and is a medium of exchange which ensures continual regulation of the internal environment. This applies to covering tissue, epithelium, parenchymas, and so on.

In bones and joints, on the other hand, everything is made of connective tissue. In an epithelial section, for instance, behind the cells aligned neatly side by side, there is an intermediate zone with a very complex structure, composed of an amorphous gelatinous substance, or *ground substance,* collagen fibres, and cells. The fibres are typical of connective tissue, the prototype of these being the fibroblast; the other cells doubtless come from the circulating blood (mainly white cells).

The synovial membrane is made almost entirely of connective tissue. It is here that the very first lesions of that terrible disease, chronic rheumatoid arthritis, occur. The lesions extend from the synovial membrane to the cartilage and then to the bone. The synovial is particularly rich in ground substance and during the last few years an attempt has been made to determine the structure of this intercellular substance. It is known that it is made of mucopolysaccharides. These are very large molecules, the basic structures of which are apparently disaccharide groups (fig. 1) arranged in long linear chains. These mucopolysaccharide chains are usually branched upon supporting protein. Albert Dorfman has described the structure of ground substance with its protein and its mucopolysaccharide chains around which a grouping of sodium and chlorine ions retains an important quantity of water (fig. 4). It is now known that the loss of the connective tissues' ability to hold

(2) *Reticuloses: These are diseases the lesions of which can affect any part of the reticulo-endothelial system; the unity of this system, which is essentially functional in adults, is due to the fact that the system retains the multiple potentialities of the embryonic mesenchyma.*

this water—that is, a loss of hydrophilia—is one of the first stages of ageing. On the articular side of the synovial membrane are cells which secrete a viscous liquid notable for its richness in mucopolysaccharides (mostly hyaluronic acid). This liquid has two functions: it provides nutrition for the articular cartilage cells, and acts as a lubricant, allowing the surface of the joints to glide over one another. Its composition is constant and, in pathological states, the study of its viscosity, and of the amount of cells and proteins, as well as the search for possible microbial contamination, is of great interest.

There is a greater differentation of connective tissue in articular cartilage. Collagen and elastic fibres are almost non-existent, and the structure is made up of special connective tissue cells, the chondrocytes immersed in a solid substance with an elasticity of its own and which is especially rich in chondroitin-sulphuric acids A and C. It is here that we see the beginning of articular senescence; the ground substance loses its natural hydrophilia and a depolymerization of the long mucopolysaccharide chains appears to occur. Paradoxically, the initial lesions of arthritis[1] appear in the deep cartilage layers. The cartilage then develops cracks, becomes eroded, and later, when the erosion reaches its maximum, the underlying bone is bared.

Bone tissue

Somewhat surprisingly, bone tissue is only of secondary importance in the study of rheumatic diseases. Lesions found in bone tissue are secondary both in rheumatoid arthritis and in degenerative arthritis (osteoarthritis).

An exception to this is when a joint becomes septic (owing to an ordinary pyogenic bacillus or a tubercle bacillus). The initial lesion is periarticular, sometimes in the synovial membrane, sometimes in the bone, and appears as a small focus of osteitis which develops towards the joint space. The progress of the lesions in each case is shown in fig. 3.

However, although a knowledge of bone tissue may be less significant in the interpretation of rheumatic diseases, it is nevertheless important because bone tissue can be affected by numerous disorders, such as metabolic disorders, tumours, and hereditary and infectious diseases. As in all connective tissue, the usual elements are present in the bone: cells, fibres, and ground substance. In the bone, the cells, or osteocytes, are a differentiation of the original fibroblasts. They are to be found deep in solid ground substance, this being particularly rich in chondroitin-sulphuric acid. Calcium salt crystals are deposited on this matrix, giving bone tissue its biochemical specificity (hydroxyapatite with the formula $Ca_{10}(PO_4)_6(OH)_2$). This ground substance and these cells are laid out almost geometrically to form rods in the bone, through which run small protein fibres identical with small collagen fibres. Bone is a tissue that undergoes a constant process of alteration and the important effects which hormones, vitamins and enzymes have upon it must be emphasized.

More recent but more diverse studies have been made on non-articular rheumatism; this term would seem paradoxical, but in fact the word rheumatism derives from the Greek *rheuma*, which means flow. With usage, this has come to be associated with the joints. In fact, the study of periarticular formations (fluid-sliding bursae, tendons, ligaments, capsules, layers of subcutaneous fat, aponeurotic lammae, etc) shows that these, like the synovial membrane, are all capable of becoming inflamed and causing pain, either in isolation or as part of an extended inflammatory disease (rheumatoid arthritis). This is not really surprising, because typical connective tissue structure is to be observed in them. But one thing must be emphasized; they are not rich in ground substance or intercellular tissue and are made up almost exclusively of intricate and tightly-woven collagen fibres. For this reason, the study of collagen fibres has been based on such tissues; under the electron microscope, collagen fibre is shown to have a characteristic periodic structure, no matter where it comes from. It has a complex chemical composition, is exclusively proteinic and is particularly rich in glycine and proline. It is the only part of the organism containing hydroxyproline, though little is yet known about the exact arrangement of the long protein chains. It appears to consist of three intertwined helical chains which ensure elasticity and firmness, both essential characteristics of these tissues.

Synovial membrane, cartilage, bones and periarticular formations appear to be the favoured points of attack by rheumatic diseases. It is one of the achievements of modern medicine to have demonstrated that if it is correct to speak of 'organs and functional units', it is also correct to speak of *systems*: while most diseases affect organs (pulmonary tuberculosis, cancers, Bright's disease, etc), there are others which are capable of affecting

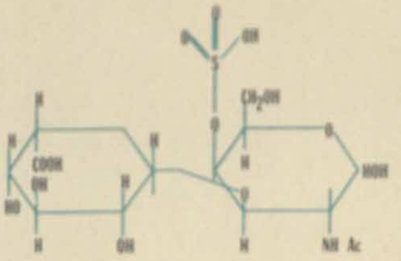


Fig. 1. Disaccharide grouping of chondroitin-sulphuric acid A. This acid forms the intercellular or ground substance.

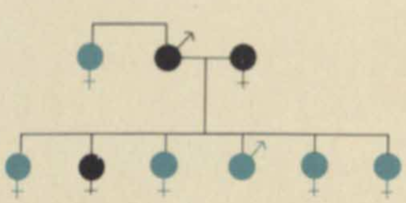


Fig. 2. Genealogical tree of a family of six children of which five are carriers of Heberden's nodes. (The blue discs show affected individuals, black those in good health.) The father is a normal phenotype, but carries the pathological recessive gene (from Heredity in Articular Diseases, *R. M. Stecher,* Doc. Rheum. Geigy, *No. 12).*

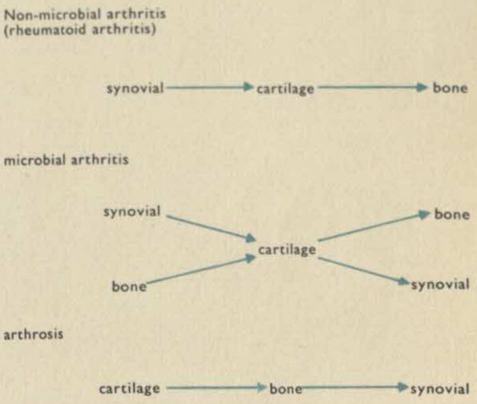


Fig. 3. Anatomical progression of lesions in each of the main articular diseases found in the pathology of rheumatism.

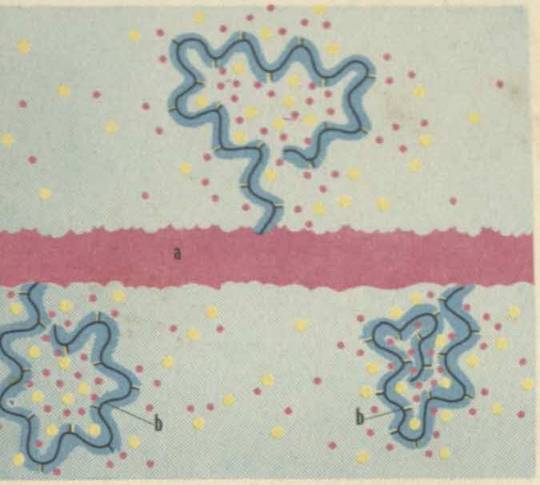


Fig. 4. Structure of ground substance with (a) protein from which branch (b) the polysaccharide chains. The yellow dots represent Cl^- ions and the red dots Na^+ ions. The background represents water in the medium (from Albert Dorfman, J. Chron. Dis. *November, 1959.)*

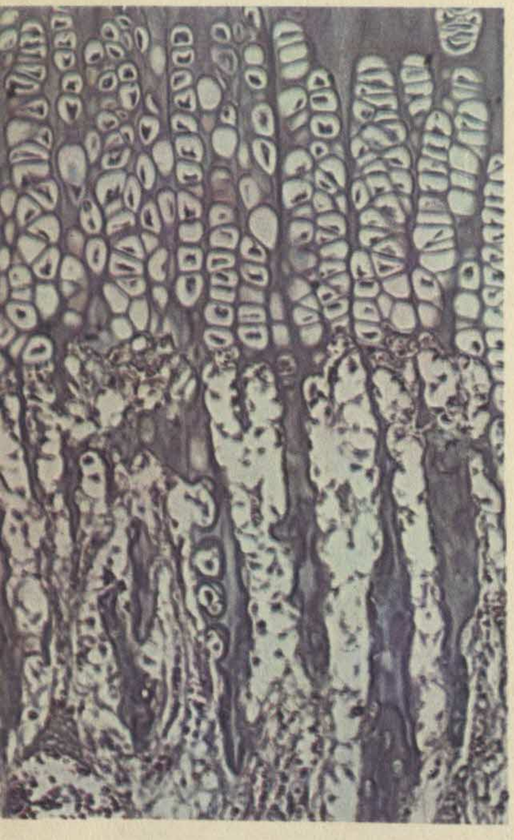


Fig. 5. Above, microphotograph of a section of cartilage tissue; below, becoming ossified. (Photo Lod).

a certain tissue situated in various organs or throughout the body. This applies to reticuloses[2] and also to certain diseases affecting a number of the glands of internal secretion. The same applies to inflammatory rheumatic diseases. Although these are most marked in articular connective tissue, they can affect any organ, according to the proportion of connective tissue that it contains. A well-known example is that of acute rheumatic fever, which attacks the joints suddenly but temporarily and is fortunately curable, although attacks made by this disease on the heart and its valves often leave serious after-effects: rheumatoid valvopathies. This is not the only example; rheumatoid arthritis, disseminated erythematous lupus, ankylosed periarthritis may show themselves in varying degrees in other parts of the organism: ocular, cardiac, polyserous, subcutaneous nodular, arterial, arteriolitic, and nephritic systems, are all subject to attacks on the connective tissue to be found in them. The discovery of this reaction of all connective tissue when subject to inflammatory disturbances has been one of the principal landmarks of recent research into the still little-known mechanism of rheumatic diseases.

Cause of rheumatic diseases

The continual progress made in our knowledge of the detailed structure of supporting tissue has not, however, so far thrown any definite light on the cause of rheumatic diseases. To speak of articular ageing in order to explain arthritis is merely to substitute one enigma for another.

What is ageing? From more than one point of view, arthritis would seem to be a genuine physiological phenomenon: skeletons of Neanderthal man (40,000 BC) show signs of it; it is also to be found in the skeletons of prehistoric animals, and symptoms comparable with those of human arthritis exist in a number of present-day animal species. In man, systematic radiological examinations show that arthritic symptoms appear during the third and fourth decades of life. In fact, by the age of fifty, all normal people have radiological signs of arthritis; fortunately, however, only a small minority suffer any damage.

As for ageing in general, many factors have been suggested to explain the appearance of arthritis: local mechanical factors, general endocrine and metabolic factors, etc. A certain hereditary predisposition would appear to exist in a number of cases. For example, arthritis of the distal extremities of the hand, or Heberden's nodules (distal interphalangeal arthroses), which are very significant, are to be found predominantly among women, in whom the disease occurs with more severe effects. Women pass on the disease to men, in whom it occurs less severely. The genealogical tree drawn up by Stecher (fig. 2) is of great interest.

Nevertheless, research on an hereditary aetiological component in other types of arthritis is a difficult matter because of the great number of aetiological factors present.

Even more mysterious is the cause of inflammatory forms of rheumatism; apart from acute rheumatic fever, certain other infectious types of rheumatism (Reiter's syndrome) and a few rare cases of arthritis, the cause of which is known (reaction to treatment, serum sickness, etc), there are a large number of cases of arthritis with diffuse inflammation of the connective tissue, the origin of which is extremely hard to decide. Numerous explanations have been put forward. The disease was once attributed to infection, but bacteriological research into articular and para-articular tissue does not support this explanation. It was also thought that local infections (dental, rhino-pharyngeal, etc) were responsible, but removal of these foci, which are at some distance from the inflamed areas, or sterilization of them with antibiotics, does not generally lead to a cure. Other explanations concern the remarkable therapeutic efficacy of cortisone and its derivatives, which would seem to confirm a nervous or endocrine origin. At present, the existence of a hypersensitivity mechanism is being suggested, a hypothesis based on the marked similarity between these diseases and their diffuse connective tissue lesions and diseases provoked experimentally in animals by creating hypersensitivity and then re-introducing the substance which had caused it (ie, the antigen). However, the origin of these appalling chronic rheumatic diseases is still obscure.

Our lack of aetiological knowledge unhappily deprives us of a logical approach to therapy: with regard to rheumatic diseases, this remains purely empirical and much too symptomatic. Although the discovery of microbes, vaccines, sera and antibiotics has little by little provided a logical answer to the etiology and therapy of most infectious diseases, no similarly satisfactory solution has yet been found for rheumatic diseases. At present, there is nothing to indicate which of the numerous hypotheses concerning their origin will give us the right clue.

The teeth

Michel DECHAUME

Much attention is rightly paid to disorders of the principal organs of the body, but some areas are neglected because disturbances in them do not endanger life. But everything in the body is important, and the same laws of pathology and physiology apply even to the most localized parts. The smooth functioning of teeth, jaws and salivary glands is essential for man, who feels pain at the slightest disturbance in any of them.

Because the teeth are living organs, it is logical, in a classification of diseases that can affect them, to follow the teaching of general pathology and hence to distinguish between *congenital* dental defects, *congenital and specifically hereditary* diseases, and *acquired* diseases.

Many *congenital* dental defects are hereditary and are explained by genetics. Some are perhaps embryonic abnormalities.[1] These can be subdivided as follows:

Constitutional anomalies of shape, number, or structure.

Eruption anomalies.

Anomalies in arrangement, direction, and position.

Anomalies of the dental arches in association with dental anomalies.

Genetics only can explain *congenital and specifically hereditary* diseases.[2] These are characterized by tissue lesions: by hypoplasia[3] or by hereditary brown-enamel dystrophy[4] (hereditary opalescent dentine).

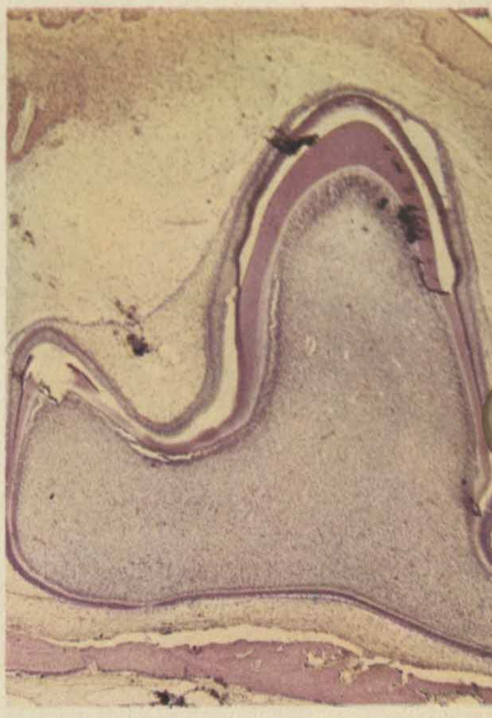
Among *acquired diseases* the following should be mentioned:

(a) Those that affect the teeth while they are being formed, especially the permanent teeth while they are still in a rudimentary state inside the jaws. When these diseases appear during the eruption of the teeth, they result only in defects. Known as *hypoplasias*, they constitute a response common to all diseases that may affect a child at the start of extra-uterine life. Only by their position and extent do they indicate the exact age at which the illness occurred and how long it lasted.

(b) Those that affect the teeth when they are in place on the dental arch. It is no longer possible to ascribe the aetiology of most of these diseases to external causes. In conformity with the laws of general pathology, acquired diseases of teeth are classed as traumatic lesions, trophic lesions, and mixed (trophic and inflammatory) lesions, and tumoural lesions.

This biological concept is not simply a matter of speculation: it is essential in order to ensure a correct approach to treatment.

It is difficult to continue in the belief that *abrasion* or *erosion* (more correctly termed *mylolysis*), whether it be on the grinding surface or on the vestibular sides of the teeth, can be caused by mastication or brushing, in the absence of a trophic disturbance, probably of neuro-sympathetic origin.



Section of tooth bud· in a cat, showing all the characteristic parts of the final tooth. Proceeding outwards, the pulp, dentine, and enamel may be seen, all enclosed in the dental sac.

Causes of caries

Caries begins with trophic disorder that allows external causes to operate; it is only secondarily that it becomes subject to infection. But it is erroneous still to believe, as some do, that it is sufficient for the tooth to have been well formed in early years for it to be protected from caries. Prophylaxis must be assured throughout life by supervision of eating habits, attention to oral and dental hygiene, and ensuring that systematic examinations are carried out carefully and regularly, at least until we know something more about aetiology and pathogenesis.

Local treatment of caries should be governed by a biological rather than a mechanical approach. Thus it is not sufficient, when decay has not reached the pulp, to remove the softened parts and re-establish the shape of the tooth by a filling. To give biological treatment before filling should, while limiting excision of diseased tissues, check the development of the pathological process wrongly called 'recurrence of caries'. When the pulp is attacked, there are therapeutic methods that allow it to be preserved or will at least keep the tooth by preventing apical infections.

Periodontal disease

Periodontosis[5] or *periodontitis*, better known as alveolar pyorrhoea, is equally responsible for the loss of a large number of teeth. Many diseases have successively been blamed for its aetiology.

Several theories have been put forward to explain its pathogenesis. It now seems that inflammation is the basic pathological process in the majority of patients, but in some it may be a complicated factor superimposed on tissue affected either by occlusal trauma or hereditary factors. But the role of the sympathetic nervous system must not be ignored. It is recognized that there is a richness of sympathetic innervation of the tissues surrounding the teeth which makes it possible for the physiopathology of 'alveolar-dental articulation' to be brought into line with that of other articulations. Thus a post-traumatic ligamentary oedema may occur in persons suffering from congenital or acquired affections of the sympathetic nervous system without apparent cause (as in allergy) or as a result of generalized traumas (dento-maxillo deformations and mastication), or localized traumas (pencil-biting, regularly repeated while working), oro-facial defects of the musculature (anomalies in swallowing and in speaking, or sucking tics, etc). This may cause mobility or protrusion of one or more teeth, which increases the articular pressure and results in increase of trauma. Disturbances of circulation then occur which cause a resorption of the alveolar bone, predisposing to the onset of inflammatory complications.

Among other local factors that are held to be of importance, faulty positioning of the teeth must be considered. But perhaps it is not so much malpositioning that should be blamed as the persistence of neuro-muscular disturbances that are to be found in 90 per cent of sufferers from periodontosis.

Dental malpositioning and malformations of the jaws

It is usual to distinguish between malpositioning of the teeth and malformations of the jaws. The former is, however, often linked with the latter. Diagnosis is not very easy, although it is essential before beginning treatment. Orthodontic treatment is usually given by means of an apparatus that exerts pressure or traction on the teeth. There are many kinds of apparatuses, both fixed and removable, but no single apparatus is capable of treating every kind of defect.

The frequency of recurrence of the disorder is a demonstration of the imperfection of present methods of diagnosis and treatment. On the other hand, a great deal of research has emphasized the predominance of generalized biological phenomena over localized phenomena. There has therefore come to be a medical orientation to orthodontics; morphology is only a visible manifestation of more subtle phenomena of a biological nature.

The problem has to be reconsidered from a biological angle, and the ideas put forward by Cauhepe and his pupils must be taken into account:

1. Teeth and jaws that form the apparatus of mastication, preserve their autonomy and their unique features, making them sensitive to specific influences. This explains the aetiology and pathology of dento-maxillofacial deformations; these are of a biological order. Subsequently, because of functional adaptation, the alteration of one part entails modifications of other parts through the musculature.
2. The bones that make up the skull and the face are of diverse phylogenetic origin.
3. During the first two months of life, overriding genetic influences produce very

(1) Embryonic abnormalities: *malformations acquired as a result of an infectious, toxic, physical, psychological, or deficiency disturbance occurring during the first few weeks of foetal existence.*

(2) *Diseases, not malformations, since these lesions develop.*

(3) Hypoplasia: *defective development in tooth-formation.*

(4) Brown hereditary dystrophy of enamel, *more often called* hereditary brown hypoplasia of enamel: *this is a dystrophy (lesion of development) that is hereditary, attacking both the deciduous and the permanent teeth, in which the teeth are brown and damage is done to the enamel.*

(5) Periodontosis: *degeneration of the supporting tissues of the teeth, leading to their destruction and the loss of the teeth, with or without inflammatory complications (periodontitis).*

(6) Asialia: *absence of saliva.*

(7) Xerostomia or aptyalism: *a notable diminution of salivation that can lead to complete suppression of secretion. It is observed during certain diseases of the salivary glands and lesions of the medulla oblongata, and certain forms of scleroderma, Mikulicz's disease, Gongerot-Sjögren's disease, and after X-ray therapy of the parotid, sub-maxillary or cervical regions.*

wide variations of form and relationship. The presence of the dental system increases these variations still further. The number, shape, dimensions and position of the teeth are also under the influence of heredity; these characteristics are not linked with those of the skeleton. On the other hand, infectious diseases, deficiencies, physical agents, etc, may cause serious disturbances.

4. From the second month onwards, all the organs are formed and grow until the end of adolescence at a progressively reduced rate. The rhythm and amount of growth are regulated by the endocrine system, and especially by the pituitary and thyroid, while the direction is determined by the muscles.

In general orthopaedics, musculature plays an essential part in the modelling of the bones that are being formed, owing to the equilibrium between antagonistic muscles. This general law also applies to alveolar processes which develop between two muscular masses; the tongue inside and the buccal and masticatory muscles outside. Thus the direction of growth of alveolar processes and teeth, together with their equilibrium, depends as much on muscular tone as on muscular strength. The latter continually exerts its effects on these structures, both at rest and during the course of many functions, such as swallowing, speaking, and mastication.

The part ascribed to muscle tone in disturbances of growth of the face, jaw, and alveolar processes, entailing multiple craniofacial malformations, is also very great. In fact, disturbances of tonus are rarely isolated and in most cases they are associated with anomalies of muscular strength or with muscle tics.

Diagnosis has to be brought to bear on anomalies and tics, since we have little means of affecting tonus. On the other hand, muscular re-education gives remarkable results.

Muscular or extrinsic forces exert an effect only on growth centres that are active. Healthy bone, once formed, is no longer sensitive to this; it must always be borne in mind that teeth, even those that are badly placed or articulated, are in physiological equilibrium because they remain stable; treatment must therefore only induce displacements compatible with this equilibrium, unless a new equilibrium can be set up.

Orthodontic apparatus can only move teeth permanently by respecting this balance. Re-education of abnormal reflexes enables the shape of the arches to be altered. If the occlusion of the teeth prevents this action, the forces provided by such apparatus are useful, as long as they act in the same direction as the muscles, which alone can ensure stability.

The temporomandibular joint, its function and pathology

The temporomandibular joint must not be thought of as a hinge; it is not made to support effort. It would be equally false to say that the lower jaw behaves like a third-order lever (the resultant of forces applied between the point of resistance and the point of support). In reality, the resultant of these forces is a complex co-ordination of the action of various muscles of mastication. Normally, this is to be found in the area of the teeth. The lower jaw may thus be considered as having muscles attached in the region of the dental arch where the resistance is to be found. The teeth bear all the force of muscular contraction; the temporomandibular joint is protected from all effort; there is no lever. As a powerful effort is brought to bear on the dental area during isometric contraction of the muscles, it is essential that the dental arches be complete and also that a definite stop should be supplied by correct dental occlusion without abnormally inclined planes. As with all joints, the jaw is richly supplied with peripheral sensory receptors, which make this region a true peripheral sensory organ.

Thus it happens that because of their repetition, traumas of the temperomandibular joint, whatever their degree of seriousness, exert a slight but continued irritation of the articular nerves and peri-arterial sympathetic system. These articular traumas have a varied aetiology. Very often, they are caused by dental occlusal disturbances. However, they may also be caused by pressures, whether as a result of unilateral mastication (because of toothache, a large tooth gap, or faulty articulation of the teeth), or by abnormal contractions (voluntary or involuntary, or tics) of the muscles that move the lower jaw and displace it forward or to the side at the same time as it is lowered. Not everyone reacts in the same way to these pressures. Some people who tolerate them without difficulty for years may suddenly become sensitive because of a concurrent disease or psychological disturbance. Then the irritation becomes a cause of neuro-sympathetic disturbances occurring either in the joint at some distance from it or, in particular, facial pain that simulates neuralgias of the trigeminal nerve.

(8) Gongerot-Sjögren's syndrome: *a syndrome of unknown aetiology in which there is diminution or arrest of tear-gland secretion and of the lower digestive tract, with keratitis, dry conjunctivitis, rhinitis, pharyngitis caused by hypertrophy, and then atrophy of the salivary glands, chronic polyarthritis and slight fever.*

(9) Mikulicz's syndrome: *bilateral hypertrophy of the salivary and tear glands, with diminution or suppression of secretion occurring suddenly without apparent cause and without local pain. These disturbances, sometimes leading to leukaemia, are of unknown origin.*

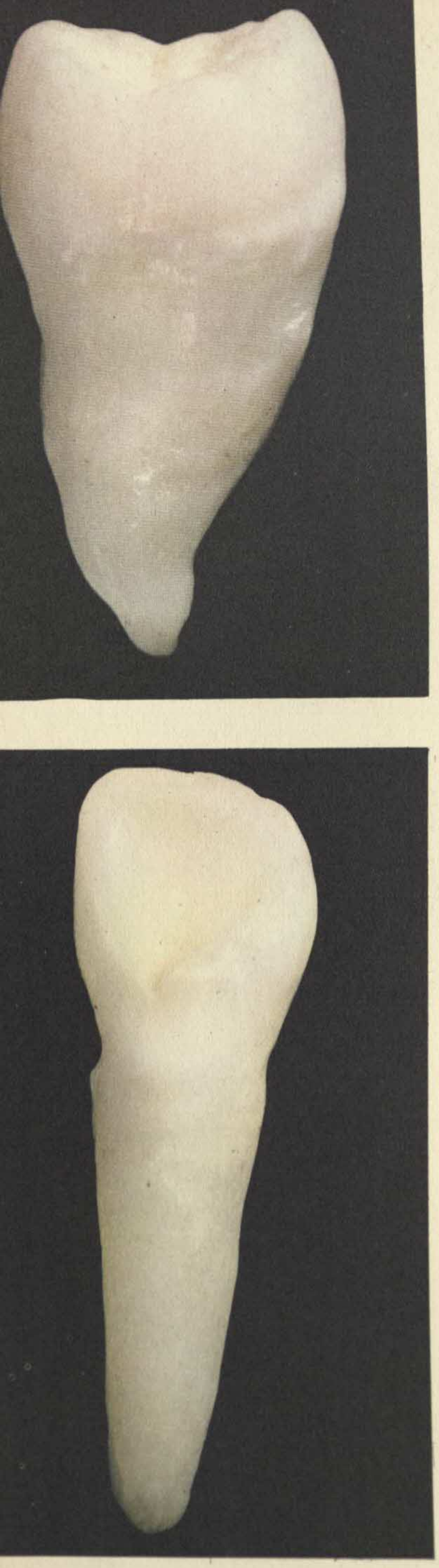
(10) Relapsing parotiditis: *recurring inflammation of the parotid gland.*

(11) Anamnesis: *information supplied by the patient or his relations on the beginning of his illness up to the moment he is in the doctor's hands.*

(12) Sialography: *radiography of the ducts of the salivary glands (Stenson's duct and Wharton's duct) after injection with a liquid that is opaque to X-rays (lipiodol).*

(13) Arthralgia: *articular pain without an appreciable lesion of the joint.*

(14) Myasthenia: *a disease characterized by abnormal muscular exhaustion of a progressive nature, increasing by steps and principally affecting the extrinsic muscles of the eye, the masticatory muscles, and the pharyngeal and laryngeal muscles; it may also extend to the spinal muscles (neck and limbs) and lead to death from motor-centre disturbances. It may be due to a progressive blocking of the myoneural junction, the aetiology of which is unknown.*



Two examples of human teeth: above, premolar with a wide masticatory surface, with two tubercles; below, incisor with upper cutting-edge bevelled.

The salivary glands and their endocrine role

The physiology of the salivary glands is very little understood. A great deal of research has been devoted to the study of the physical properties and chemical composition of saliva, but unfortunately no valid deductions have yet been drawn concerning its physiopathology.

In considering the mechanism of salivary secretion and its disturbances, it is necessary to consider the important part played by the large glands (the parotid, sub-maxillary and sub-lingual glands). It seems, however, that accessory glands disseminated in the mouth cavity contribute largely to maintaining the moistening of the mucosa.

The pathology of salivary glands includes, besides well-defined diseases (swelling, calculi, inflammatory affections, malignant and benign tumours), some curious diseases about which we are very badly informed. Nor does cytology throw much light on the diagnosis of them. They include asialia,[6] xerostomia,[7] Gougerot-Sjögren's syndrome,[8] Mikulicz's disease,[9] relapsing parotiditis,[10] and bilateral parotid hypertrophy. The latter is characterized solely by an increase in size. During anamnesis,[11] or clinical examination, endocrine disturbances may sometimes be found in the ovaries, pancreas, thyroid, or liver, and sometimes a general disease can be discovered. Often, however, there is no explicable cause. Sialography[12] gives the same sort of picture whatever the aetiology, for it only provides information on the anatomical condition of the gland. Whatever the aetiology, biopsy shows the same mode of affection of the tissues; de-differentiation of the acini, which are of the mucous or canalicular type, modification of the ducts, the walls of which become irregular and thicken so that the lumen tends to disappear, the formation of myo-epithelial islets, and the appearance of more or less abundant infiltrations. The intervention of the sympathetic nervous system would appear to be a very probable factor in the production of lesions.

This hypothesis must be related to the hormonal role that Japanese and Rumanian research workers attribute to the parotid and submaxillary glands. Experimental work in animals shows that:

> Certain relationships exist between salivary and endocrine glands (the genital, pituitary, pineal, thyroid, and suprarenal glands);
>
> Removal of one salivary gland in an animal causes modifications of the other salivary glands.
>
> Experiments have also demonstrated the role of salivary glands in the metabolism of glucosides and their relations with the pancreas, as well as the presence of enzymes in the salivary glands.

Clinical research has shown the existence of parotid hypertrophy in cirrhosis, ethylism, and diabetes, as well as the favourable effect of hormonal treatment in certain diseases of the salivary glands.

In 1926, Tomasaburo Ogata showed experimentally that salivary glands have an endocrine as well as an exocrine activity. This endocrine activity causes diminution of serum calcium, a phenomenon that is interpreted as the result of the transport of serum calcium to bones and teeth, causing an acceleration of growth. Parotine or parotid extract is an accelerator at a weak dose, an inhibitor and then an accelerator at a medium dose, and an inhibitor at a strong dose.

Further Japanese work has confirmed these views and has led to the conclusion that salivary endocrine function ensures the proliferation of the mesenchymatous tissues; that is to say, cartilage, bone, teeth, elastic fibres, reticulo-endothelial system, and connective and haematopoietic tissues. Diseases that appear to be caused mainly by a disturbance of endocrine function are combated by injections of salivary hormone.

'Parotine' is now available in Japan; it is a hormone extracted from mammal salivary glands—in particular the parotid, by a special process—and crystallized by refrigeration.

The syndrome caused by a deficiency of parotine is characterized by the softening of cartilage in the foetus. This deficiency causes a cartilage dystrophy that prevents the development of the bones of the limbs. In adults or old people, lack of parotine causes painful, deforming arthritis, associated with ankylosis of the limbs and the hip and also with spondylitis. Parotine would appear to be efficacious in the treatment of these diseases. It would also appear to have a beneficial effect on senile cataract, arthralgia,[13] myasthenia,[14] muscular atrophy, deafness of senile or drug-induced origin, periodontosis, lumbago of pregnancy, and a number of skin diseases.

Nitzesco and Stanesco have shown experimentally that the parotid hormone produces a diminution of secretion of the gastric juices and of salivary secretion.

Human cancers

Pierre DENOIX

Recent research on cell and tissue grafting has shown that the anatomical form and development of cancer vary according to the biological relationships that exist between the tumour and the organism that bears it; this host-tumour relationship leads to the notion of treatment designed to moderate and even to stop the activity of the cancerous cells. But despite an immense amount of research, the origin of cancer in man is still unknown, although it is possible to cause cancers in animals by various means. What is the common denominator of these carcinogenic agents? Is it a direct or indirect action on the nucleic acids contained in the cell nucleus which constitute the fundamental element in its genetic make-up? In this chapter questions such as these are examined from a very general point of view.

Human cancers, in the diversity of their symptoms and their seriousness, represent the various aspects of a general disease,[1] usually manifested by a primary tumour[2] developing in the organ where the disease first occurs. The appearance of such a tumour is often associated with the development of other foci composed of malignant cells similar to those of the main tumour. These foci constitute what are known as metastases and are situated either in the lymph nodes or some distance away.

The development of a cancerous disease may occur in various ways. There are many possibilities, ranging from regular progression to spontaneous regression, going through successive stages of development. The rhythm of this development, which conditions the seriousness of the localization and the prognosis of the disease, is determined both by the developmental potential of the malignant cells composing the tumour and by the reaction of the organism in which it occurs. Each cancer finds its developmental rhythm in the result of the host-tumour relationship. Most research on human cancer is centred on the problem of these relationships and on studying the way in which the organism may defend itself.

Therapeutic possibilities

The modern treatment of cancer is based on the suppression of the main focus, but has no real effect on the outlying foci. It is clear, therefore, that the success of treatment depends essentially on the way in which the organism has been able to defend itself or may be able to do so in order to oppose the development of metastases.

The future of cancer treatment depends on means of facilitating this defence in the organism, using the classical but somewhat clumsy methods of surgery and radiation treatment to remove the main tumour in the hope that 'the remainder', that is, action on other foci, will be achieved in other ways.

This conception of cancerous disease resulting from host-tumour relationships and the concept of the importance of general treatment that follows from it are relatively recent. Cancer therefore also takes its place within the framework of general pathological processes,

(1) *The idea of cancer as a general disease may be held to apply to those forms of cancer to be found in the haemolymphopoietic system; that is, the blood and the organs forming it (chiefly bone marrow), the lymphatic system being involved chiefly in lymph nodes, etc.*

(2) *Cancers may be classified according to the organ where the main tumour is to be found—the location often determines its seriousness—or the tissue where it started. In this case, they are mainly classified as epitheliomas (eg, starting in the skin); cylindrical epitheliomas (eg, starting in the stomach mucosa); sarcomas (eg, osteosarcoma in bone); leucoses (eg, myeloid leukaemia, starting with the white blood cells).*

of which tuberculosis is an example; this disease is now controlled by means of general treatment, leaving it to the surgeon in some cases to remove the residual focus of infection.

However, in the case of cancer we do not yet possess the equivalent of the new preparations used against tuberculosis; but it is in the direction of general medication that future progress may be hoped for in the treatment of cancers.

At present a steady improvement is to be seen in the results of classical treatment. Statistics show that during the last twenty years the number of cured patients has risen from one in four to one in three. This progress has not been due to the introduction of any entirely new treatment, but simply to the improvement in the application, comfort and effect of classical treatment (surgery[3] and radiation therapy[4]) which at present are the sole means of curing cancer.

The word 'cure' must be kept in perspective. It is traditionally admitted that only when a patient does not relapse within five years from the end of treatment is it possible to speak of a cure. In fact, a new focus of cancer may show itself at any time after treatment; but the probability that this will occur after the end of the fifth year is very unlikely.

After this length of time, five to six per cent of former cancer sufferers may show a new manifestation of cancer. This, of course, may also be controlled.

Frequency of cancer

The frequency of human cancer is measured by the number of new cases appearing during the course of a year in a known population; in a population of 100,000, the rate may be estimated at around 300. This means that in a town of 100,000 inhabitants approximately 300 new cancers will appear each year.

A certain number of factors may influence this rate. If the population is divided into groups according to sex, the rate, although very similar, is not exactly the same, because the main localization of cancerous disease are not the same in men as they are in women, and the greater longevity of women increases the frequency.

As a general rule, cancer frequency increases with age; however, after the age of seventy, the curve, which ascends regularly up till then, has a tendency to flatten out slightly.

Localization of cancer

On examination, cancer localization frequency curves are not strictly comparable. In cancer of the skin, for example, within the average length of life the frequency increases regularly without any flattening out of the curve. In other cases, however, such as bone cancers, not only is there a flattening of the curve, but even the start of a lowering of it, which seems to indicate in this case that the maximum frequency occurs within the average expectation of life; if life expectancy were prolonged, it should be possible to determine the trend and to see the frequency of this form of cancer diminish.

The fact that the average frequency of cancer, whatever its localization, increases regularly with age explains the necessity for taking into account the age-composition of the populations being studied, if the frequencies observed in such populations are to be compared.

When, for one reason or another, a population includes a majority of young people, the number of cancer cases is lower than in populations with a higher average age. For example, cancer appeared to be rare among the Negro populations of Africa, until it was realized that the average age of the populations of this region of the world was thirty years less than that of the white population of Western Europe. This difference in the expectation of life is sufficient to explain the fact that for every case of cancer found among the Negro population of Africa, seven are found in Europe.

It should be noted that in their relative frequencies and in relation to each other, the various foci of human cancers do not present a uniform picture throughout the world. Great differences in frequency exist for different localizations of cancer; nevertheless, provided that a given population is not exposed to some particular risk of abnormal intensity, it is observed that, on average, in two populations of the same age and sex composition, world frequency of cancer is relatively comparable. Thus it would appear that cancer risk is more or less constant in a given population, but that the relative importance of localizations may vary—probably in accordance with different ways of life.

The localization of the disease in persons predisposed to cancer will depend on whatever it may be that will reduce the resistance of the organ that will become affected, or expose it regularly to an irritant. Nevertheless, in our present state of knowledge it is very difficult to define, for any particular localization, the causes that might have promoted cancerous

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(3) *The possibilities open to surgery have considerably increased, owing to the progress in anaesthesia and resuscitation.*

(4) *The sources of radiation at the disposal of medicine are numerous and their strength, precision, and ease of use are increasing every day. These sources are: classical X-ray apparatus (200 to 300 electron-volts); linear accelerators (1,500,000 electron volts); cyclotrons or circular accelerators (10 to 35 million electron volts); natural sources (especially radium); artificial radio-isotopes of cobalt, phosphorus, iodine, gold, yttrium, etc.*

disease in an organ. The difficulty lies in the fact that the necessary statistics are subject to numerous errors, and that there are not enough systematic investigations on which conclusions can be based. In addition, there is the fact that there is no single cause and that each human cancer is usually the result of several causes which, added together, manifest cancerous processes.

There is, for example, a correlation between cancer of the bronchioles of the lungs and the use of tobacco, but this habit is certainly not the only cause; otherwise, all smokers who smoke more than a certain number of cigarettes would have cancer of the lungs, which is far from being the case. On the other hand, the fact that there is very little cancer of the lungs in non-smokers shows that, in association with other causes, this habit probably plays a part.

The influence of external factors

Possible relations between external conditions and the appearance of certain cancers are apparent, but we still possess only general indications, some quite clear, others doubtful, requiring more precise investigation.

Certain facts appear to be valid, but they are subject to dispute and still have to be confirmed. Such is the suggestion that primary cancer of the liver, which is very frequent in Africa and in certain regions of Southern Asia, is related to feeding habits and to the importance of attacks on the liver by viral or other factors common among young people in these regions.

It would appear that cancer of the breast and of the neck of the uterus have a close correlation with sex hormone activity, and that this may vary according to social and economic conditions; a rise in the standard of living of a population leads to changes in its behaviour, such as a rise in the age at which its members marry and to a diminution in the number of births; simultaneously, there tends to be a diminution in cases of cancer of the uterus and an increase in cancers of the breast.

An abnormal frequency of cancers of the oesophagus has been observed in Africa and in South America, and a high frequency of cancers of the stomach in Japan and Indonesia. It has been thought that the method of cooking food and the temperature at which it is absorbed may play a part, but this has not yet been proved.

Certain cancers of the skin are certainly related to exposure to sunlight, but these are mostly to be found in white-skinned persons.

Although all these data are more or less reliable, none of them up to the present has an absolute value, but they are nevertheless of great importance and explain the recent development of a new aspect of human cancer research—geographical pathology.

By making enquiries in the field of geographical aetiology,[5] first using facts that have been gathered empirically, and then conducting the enquiry according to strict methods, it is possible to form an idea of the factors influencing the appearance of various localization of cancerous disease. When it becomes possible to put forward precise facts leading to the isolation of a causal factor, a first step will have been taken in the prevention of cancers, as has already been achieved in the specialized and very limited case of occupational cancers; for there are, in fact, certain cancers that affect workers in certain industries. The diminution, though not the disappearance, of these cancers has been achieved by taking precautions to prevent workers from coming into contact with dangerous chemical substances. For example, cancers of the bladder in workers in the dyestuff industry are now diminishing.

Immediate and intermediate risks

Cancer risk must be considered from two angles. The 'immediate' risk concerns the chance that a person of given age has of contracting cancer in the following twelve months. It is possible to say that unless that person lives in an environment where there is a particularly dangerous factor, this risk has not altered during the last few years.

Quite different is the 'intermediate' risk of cancer run by a person between the moment the question is asked and the end of his life. This risk has increased since the beginning of the century, for the simple reason that the expectation of life is markedly higher now than it was at that time.[6] An individual therefore has more time ahead of him to allow cancer to develop.

In itself, the danger of cancer has not increased, but since each of us lives longer, the chances that we may one day be attacked are greater because the period during which the risk may occur has lengthened.

In a European population, the present risk of a newborn child[7] one day developing cancer is in the region of 22 per cent for a boy and 25 per cent for a girl. This rate is maintained with age; it is estimated that at forty-

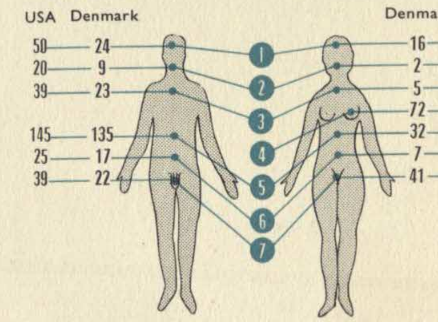
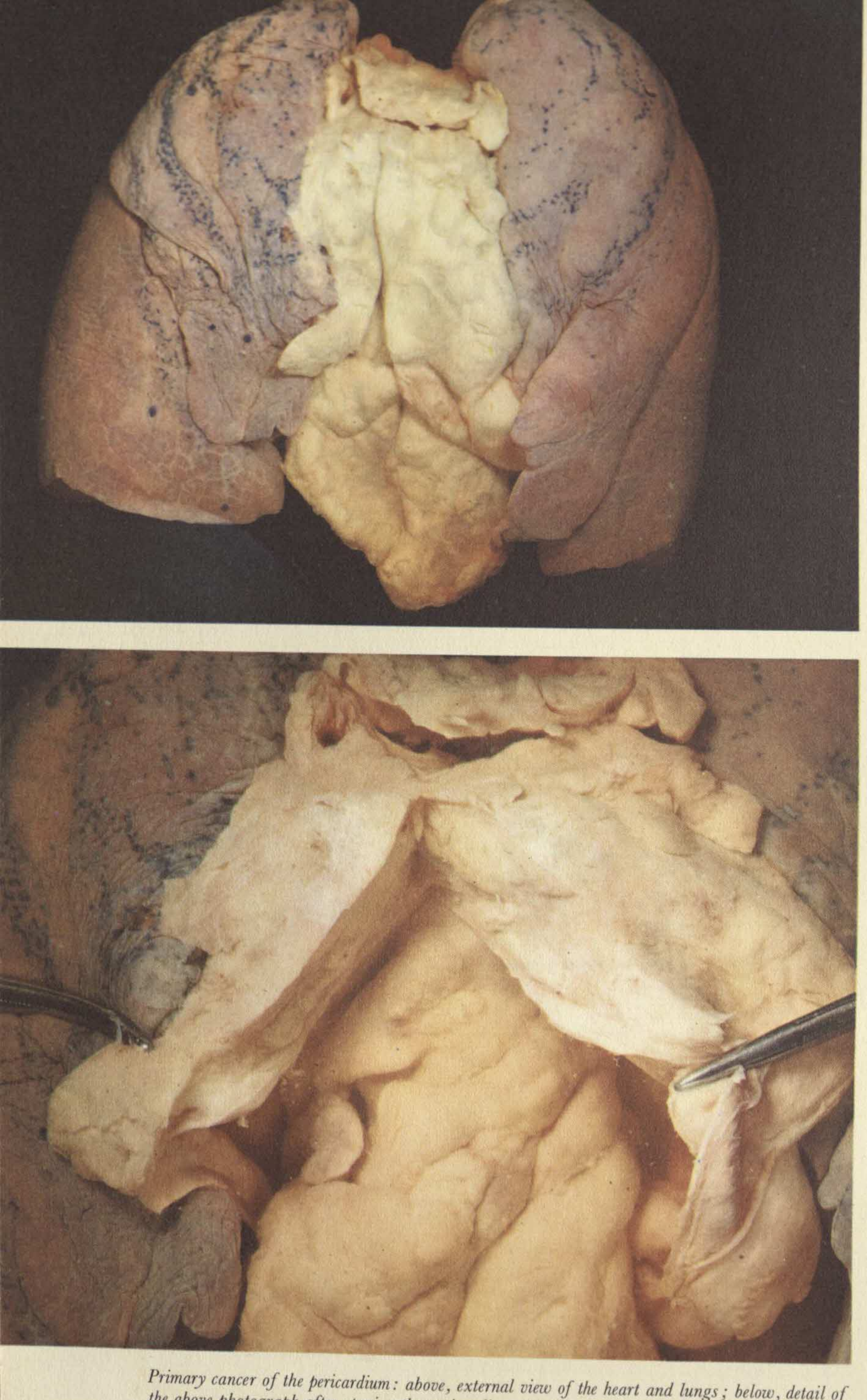


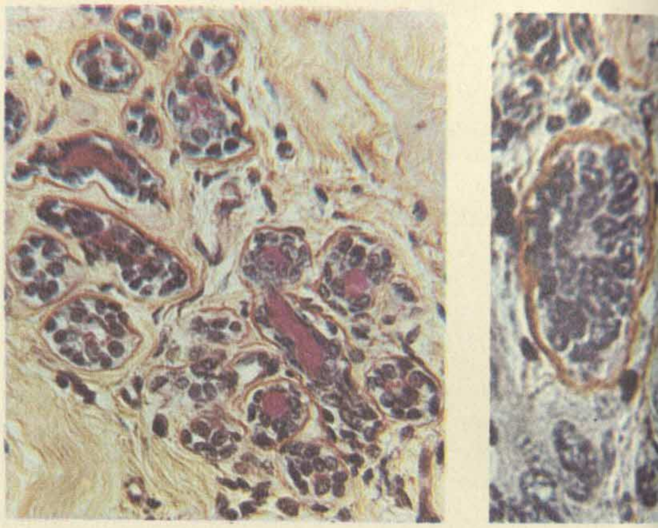
Fig. 1. The main sites of human cancer in Denmark and the United States in both sexes. 1, skin; 2, mouth; 3, respiratory system (larynx, bronchi, lungs); 4, breast; 5, digestive system (stomach, liver, intestine); 6, urinary system; 7, genital organs.

(5) *There are two main types of aetiological enquiry: 1, retrospective enquiries based on questions to patients and groups of healthy persons serving as comparative controls (here the difficulty lies in finding suitable individuals as controls); 2, 'prospective' enquiries based on questioning a sample population, in which one waits for and then registers the expected event each time it occurs—in this instance, cases of cancer. One then compares the characteristics already registered in the group of patients with those of the others. The second method, theoretically the best, is also the slowest and the most expensive. The choice of method will depend basically on the nature of the phenomenon studied and on the means at one's disposal.*

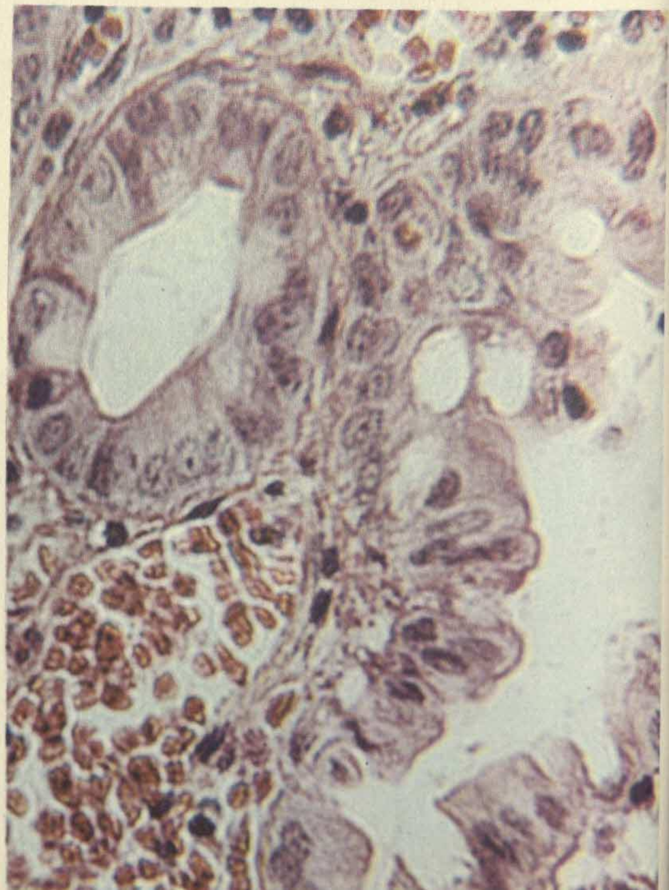


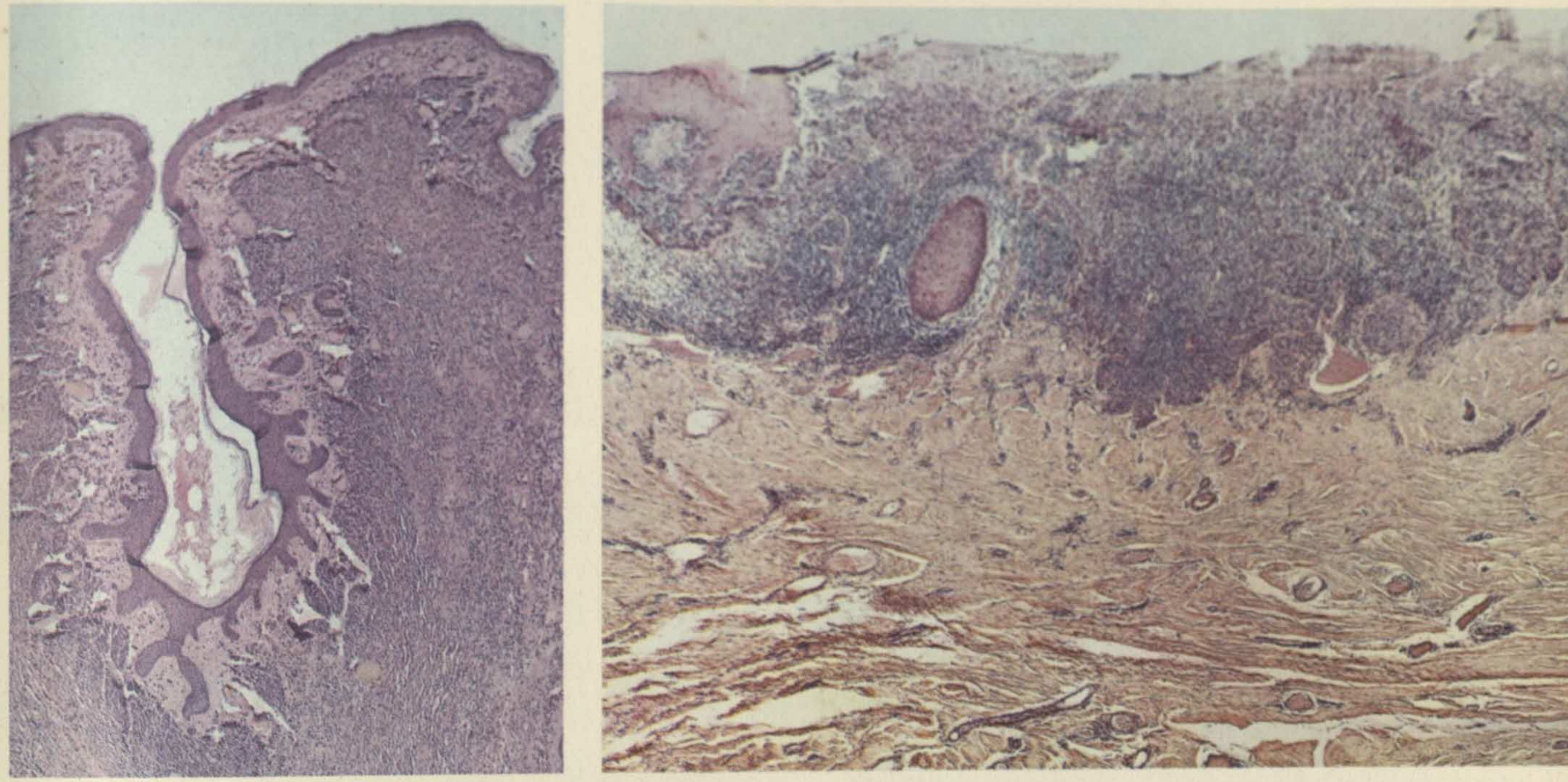
Primary cancer of the pericardium: above, external view of the heart and lungs; below, detail of the above photograph after opening the pericardium; the heart is shown already affected by cancer and covered by a neoplastic sheath. (Serrurier preparation).

Different sites of cancer

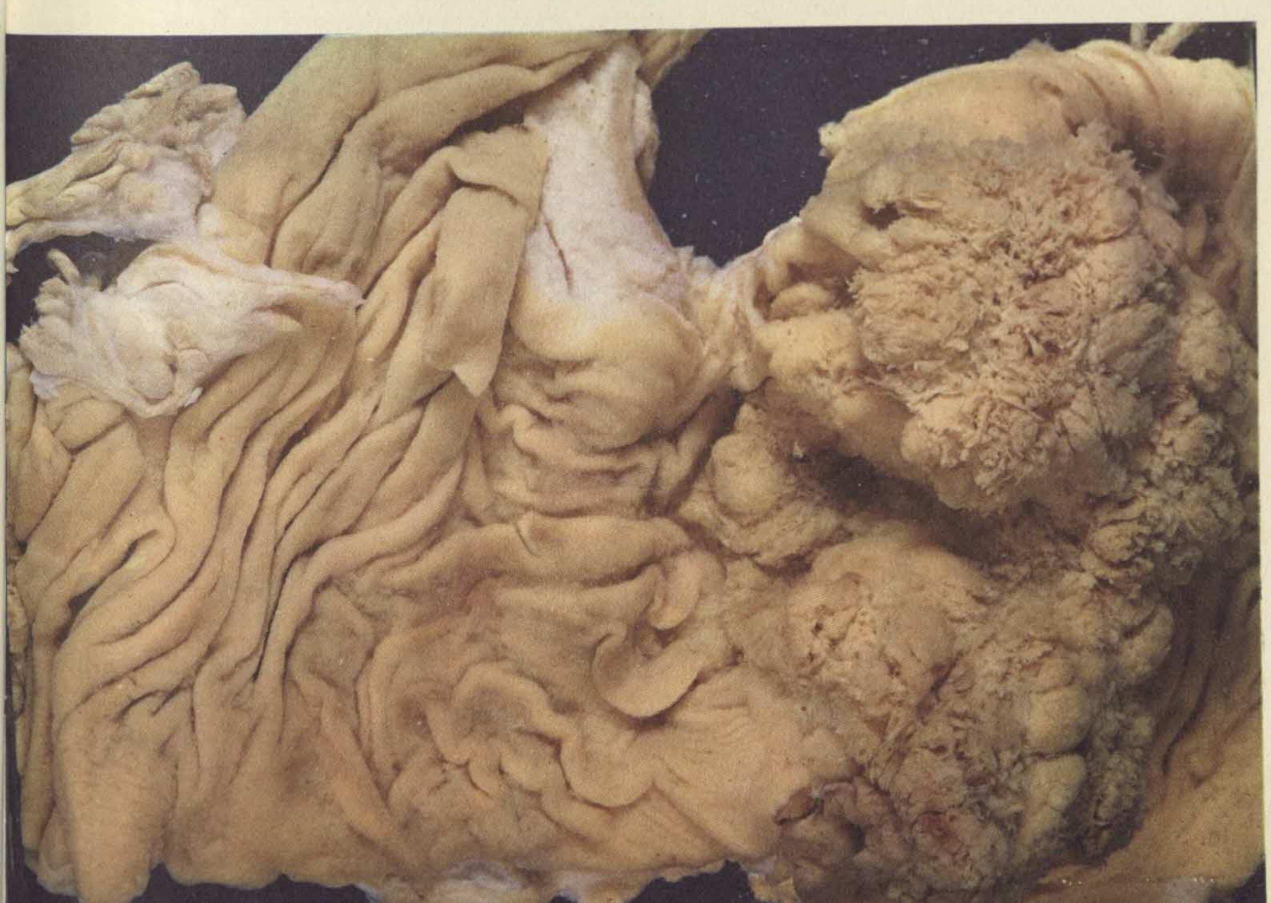


Cancer of the breast. On the right, milk ducts already show abnormal proliferation (mag. × 500), although their structure is still recognizable. On the left, a typical cancer. Malignant cells have completely invaded the tissue.





Skin cancer. On the left, a section of epidermis showing a scar from a burn; there is no cancer lesion, but this may occur and give the tissue the appearance shown on the right (carcinoma). The upper deeply stained margin corresponds to a proliferation of cancerous cells filled with pigment; the epidermis is very ulcerated (mag. × 42).



Stomach cancer. The photograph on the left shows a histological section of the gastric mucosa becoming cancerous. On the left and at the top of the illustration, the glandular tube is still normal. On the right and at the bottom, the cells of another tube show disordered development (mag. × 800). The photograph on the right shows a spreading cancer of the stomach. (Photos Lod).

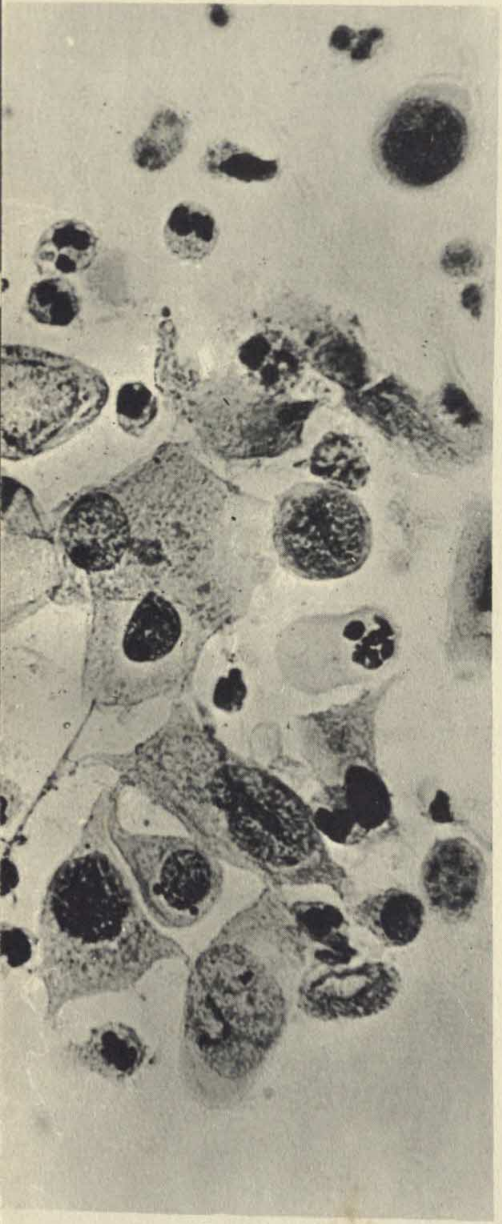
five the risk for a man is 22 per cent and for a woman 24 per cent.

It is known that cancer frequency increases with age, so it may seem surprising that this risk remains constant. In fact, we are dealing with a different phenomenon.

Suppose that a hundred persons aged forty-five have before them forty years of life, expectation of death being at eighty-five. During this period, twenty-two will have cancer, while a hundred persons aged sixty-five, with an expected life span of eighty-five, have only twenty years of life before them, during which twenty-one cases of cancer will appear. The risk is the same, but as the time is half as long, twice as many cancers appear during this period, which corresponds to the increase in frequency of cancer with age. It is possible to draw up a scale of magnitude with the risk of different varying localizations of cancer. These figures apply only to populations with a demographic, economic and social development similar to that of Europe.

In these conditions, the probability is that out of one hundred new-born boys, approximately eight will ultimately develop cancer in which the main tumour will be in the digestive system, three will develop cancer of the skin, one cancer of the lungs, one cancer of the prostate, and nine will develop it in other parts of the body, making a total of twenty-two. It must be emphasized that without counting on any new developments in treatment, seven of those twenty-two will be cured.

Out of one hundred new-born girls, seven will one day have cancer of the digestive tract, four cancer of the breast, three cancer of the genital organs, and three skin cancer. Eight other cancers will appear in different organs. Among the twenty-five girls destined to have cancer, eight will be cured by present methods of treatment.



Epithelioma of the neck of the uterus detected in a cervical smear after Papanicolaou staining. (Photo Dr R. Robineaux).

Detection of cancer

A number of erroneous ideas are regularly circulated concerning cancer. Cancer is not contagious and up to now nothing indicates that persons living in contact with cancer, or even looking after those suffering from it, are exposed to any danger.

Cancer is not hereditary. An infant whose father or mother has been or will be attacked by cancer runs no greater risk of developing it himself than if he had no such antecedents.

Cancer 'houses' have often been mentioned. Reliable investigations have failed to prove the existence of such houses. If a comparison is made in a sufficiently large residential area, it may be seen that there is no special incidence of cancer other than that arising from random occurrences.

The detection of cancer does not yet include methods as easy as those enabling tuberculosis, for instance, to be diagnosed. A socially acceptable method of detection should cause the least possible inconvenience to those involved, because, as they are assumed to be in good health until shown to be otherwise, the whole population would need to be examined. Interpretation of results would also have to be easy, certain, and rapid in order to make the system as comprehensive as possible and to diminish the cost. Nevertheless, detection must be applied to the whole population and not only to diseased persons. Thus, for example, in order to detect 300 cancers, 100,000 people would have to be examined.

Detection is at present based on a careful examination of any person believing himself to have cancer, or in certain cases, of whole communities; but the cost of this is very high. It must be added that the relatively late period in the long history of a cancer when such detection is possible does not make mass examinations helpful.

Whatever the rhythm of development particular to each cancerous disease, it is necessary for patients to confide in their doctor as soon as possible, but this does not mean that early detection of a cancer, and still less that urgent treatment, is sufficient to guarantee results. The quality of treatment and its adaptation to each particular case is much more important than the rapidity with which it is begun. It is better to treat carefully than quickly.

Matters will change, however, especially when we have a better understanding of the way in which cancer develops. We may then be able to detect cancerous disease well in advance of what we now call the 'first symptom'.

For every cancer that reveals itself for the first time, even if it appears to be quite small, there will have been a long period during which the process that 'emerges' has been developing in the organism, not only at the point of origin in the organ first attacked, but also in other parts of the body attacked by malignant cells. These cells will sometimes be destroyed by defence reaction, sometimes only made latent, and they may 'wake up' after several years, giving rise to the development of a new focus, possibly coinciding with a decrease in the patient's resistance. In other

(6) *Between 1901 and 1953, the following variations in expectation of life in two European countries were observed in persons over sixty-five:*

England and Wales

Men		*Women*	
1901	1953	1901	1953
4·2%	9·5%	5·1%	13%

France

Men		*Women*	
1901	1953	1901	1953
7·6%	9·5%	8·7%	14·1%

words, when we see cancer for the first time under the conditions which now enable us to detect it with our limited means, most of the processes in the dissemination of the cancerous disease have already been determined. This explains the limited possibilities available to us. We intervene only in the last chapter of a long story which we could only have changed by intervening at a much earlier stage, when it was still unknown to us.

Cancers induced in the laboratory

Although we do not know the exact nature of the phenomenon that occurs in the cells where the malignant change takes place, we are able to induce cancers in laboratory animals.

In one sense we are like a child who turns a switch and lights an electric lamp without having any idea of what electric current is. A great number of 'switches' of different kinds are at our disposal, allowing us to induce the appearance of cancer. Without knowing what we are starting, we can induce a lesion in which there is an accelerated and anarchic multiplication of one or more cells. The agglomeration of multiplied cells constitutes a new entity, a cancer opposed to the organism that has given rise to it. This is an event at cellular level, which, once it occurs, is perpetuated in the descendants of the cell or cells where it took place. A spontaneous return towards a normal cell, although possible a short time after the event, rapidly becomes exceptional.

It is usual to use the word carcinogenic to designate any agent or exposure leading to the appearance of the phenomenon. This carcinogenic agent may come from outside (eg, ultraviolet rays, ionizing radiations, and certain chemical substances, etc), or it may appear in the internal environment in which the cell lives (such are hormonal disturbances, or local trophic modifications).

The action of these carcinogenic agents can show itself in numerous ways, usually in several stages, between the moment when the organism is attacked and the appearance of the anarchy that provides the evidence for the cancerous cell transformation.

It is very probable that this development consists of a modification of the genetic system of the cell, affecting the nucleic acids. This action may occur in one of two ways: either the carcinogenic agent acts directly on the nucleic acids and leads to a chemical modification giving rise to cell malignancy; or it acts indirectly, going through several stages before resulting in this process of modification which appears to be the final stage common to all cases and essential for the manifestation of the phenomenon.

The point of origin of this last stage is not clearly localized in the cell; it is possible that a number of points of impact are left to the choice of the aggressive agent, and they may depend on the nature of the latter and on the receptivity of the cell. These points of impact are:

(a) The chromosomes, constitutive elements of the cell nucleus, composed of deoxyribonucleic acid. They constitute the basis of heredity and it is known that damage to the chromosomes modifies the behaviour of the descendant cells, to which this modification is transmitted from one generation to the next.

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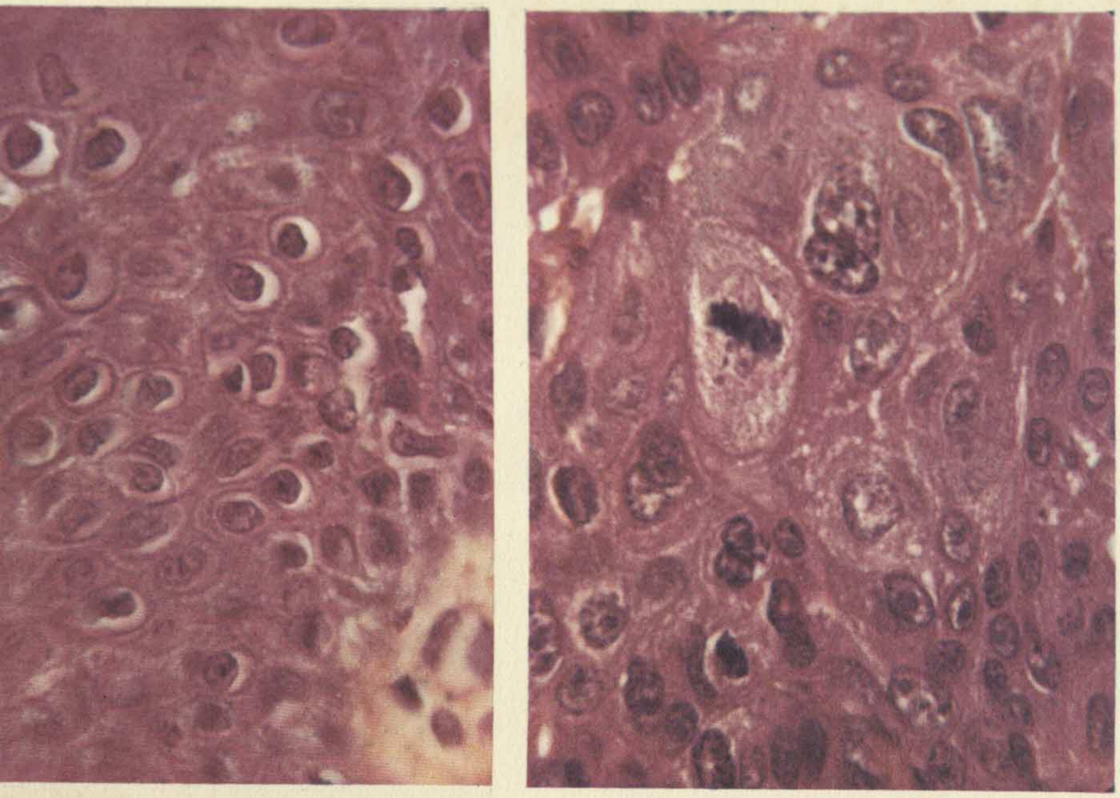
(7) *The calculation of risk in a hundred persons of a given age; it shows the number of those who will eventually be attacked by cancer. The probabilities at different ages are:*

	100 Men
at birth	*22%*
20 years	*22%*
45 years	*22%*
65 years	*21%*
	100 Women
at birth	*25%*
20 years	*26%*
45 years	*24%*
65 years	*19%*



Section of epidermal cells, normal on the left, cancerous on the right. It will be noted that in normal epidermis the shape and volume of the elements composing it are equal; the nuclei are at rest; the ratio between volume of nucleus and cytoplasm is constant. In cancerous epidermis, the cells are of variable volume, strangely shaped, and the nucleus-plasm ratio is not constant. The cells are actively dividing, and numerous nuclei are dividing. (Mag. × 1,000. Photo Dr Rémi Gérard-Marchand, histopathology laboratory of the Institut Gustave-Roussy, Villejuif).

(b) The nucleolus, situated in the nucleus, whose role in cellular division appears to be important. The nucleolus contains ribonucleic acids and it is here that the hereditary chemical modification may occur which is apparently required for the emergence of cancer.

(c) A third point of impact may possibly be found in the cytoplasm itself, in the elements called microsomes, which also contain ribonucleic acid and may equally well play a part in cellular multiplication.

It may be considered that every cell possesses two essential functions: reproduction or cellular division, and differentiation. The equilibrium between these two functions is decisive for the way in which the cells of the organism act together in the different aspects of life. A number of proteins that are formed among other things from nucleic acids, take part in one or other of these activities. The modifications caused by a carcinogenic agent would result in directing the internal system of the cell in such a way that cellular division is accelerated at the cost of differentiation.

Carcinogenic agents

Whatever the exact nature of these phenomena, which we have considered in broad outline, and are the object of present-day research, we must now consider the different agents that may directly or indirectly induce these modifications. These agents will be mentioned in order of increasing complexity in the cancerous process.

Skin cancers have been induced in animals by ultra-violet radiation, as a result of the hypothesis that skin cancer in man may be related to exposure to the sun of parts of the body not protected by clothing—parts where cancer is more usually localized.

There is a great difference, of the order of one to seven, between skin-cancer frequency on the backs of the hands and on the face, and that of cancers appearing in parts of the body that are covered. It is also to be noted that this skin cancer is exceptional in pigmented races, especially in Negroes. However that may be, experiments have shown that it is possible to induce the formation of skin cancer in depilated areas of mice subsequently exposed to ultra-violet rays.

It is interesting to note that there appears to be a relation between dosage, duration of exposure, and frequency of appearance of these cancers. In a group of mice subjected to ultra-violet radiation, the number of cases increases regularly with dosage and duration. If the experiment is prolonged, and the mice live a long time, only some of them will be resistant. In these it appears that no cancer can be induced, whatever the dose and duration, but their number is proportionately very low. This leads us to believe that in man a certain number of cancers due to direct action of external origin will increase regularly with age, as is indicated by the curves of such frequencies, and that within our present average life-span we have not yet reached saturation point, from which point onwards no cancer will appear, whatever the dose.

Ionizing radiations are also capable of producing experimental cancers. The first cancer induced in an animal was obtained in 1910 by a Frenchman, Jean Clunet, who used X-ray apparatus.

If mice are subjected to radiation, leukaemia can be induced. Experiments show that there must be a relation between dosage and duration; it even appears to indicate that there is no threshold; that is to say, a minimal dose below which cancer would certainly not appear. It has already been mentioned that cancers appear in radiologists who have, in the past, used insufficiently protected apparatus from which they have received weak but repeated doses of X-rays over a long period. The same applies to the Japanese who were exposed to atom bomb explosions, in whom an increase in the frequency of leukaemias has been noted—an increase probably linked to this kind of exposure.

A whole series of chemical substances will cause experimental cancers. Historically, it is coal tar which, when used in regular applications on rabbits' ears, led, in Japan in 1915, to the first chemically-induced cancer. The problem then arose of discovering which was the dangerous substance in a complex mixture such as tar; it was in 1930 that 3-4 benzpyrene was isolated, and then a little later, methylcholanthrene. These are still the two principal substances used in laboratories to induce the appearance of cancers by external application subcutaneous or intravenous injection, or even by oral administration.

With regard to the action of chemical substances, it must be emphasized that an agent that is known to be carcinogenic does not always lead to a positive result and that success is governed by a certain number of factors, the main ones being:

1. The *species* of the animal, since a substance may be carcinogenic for a mouse, but not for a rat or a guinea-pig;

2. The *solvent* used, because although certain solvents may facilitate the penetration of the carinogenic substance into the body (oils or fats), others may retard or prevent such penetration;

3. The *duration* of the experiment: the animal must have a sufficiently long life to permit the carcinogenic substance to show itself; in some cases the process starts very early, though external manifestations are late in appearing.

4. The *diet* given to animals used in the experiment; certain carcinogenic substances do not act if the composition of the diet is modified in certain ways, ie, either increased or decreased.

Such ideas are extremely important with regard to human cancers. On one hand, they show that while a substance may not be carcinogenic in a laboratory animal, it may be carcinogenic in man; on the other, because a substance is carcinogenic in an animal, it does not mean that it will also be carcinogenic in man. In this case, however, it is clear that any substance showing itself to be dangerous to an animal should be avoided as far as possible by man.

Any new chemical element introduced into our environment must be the subject of careful laboratory study on several series of animals of different strains and involving the use of variable doses, as well as different means of penetration, in order to eliminate those that are shown to be carcinogenic.

We have mentioned the possibility that diet might to some extent influence the action of a carcinogenic substance. We should also point out that cancers can be caused in an animal by a simple modification of diet, either as a whole in regard to its energy-content, by excess or deficiency of calories, or simply by changing one or other of the elements in the diet. Thus it has been possible, without introducing any particular substance, to induce experimental cancers.

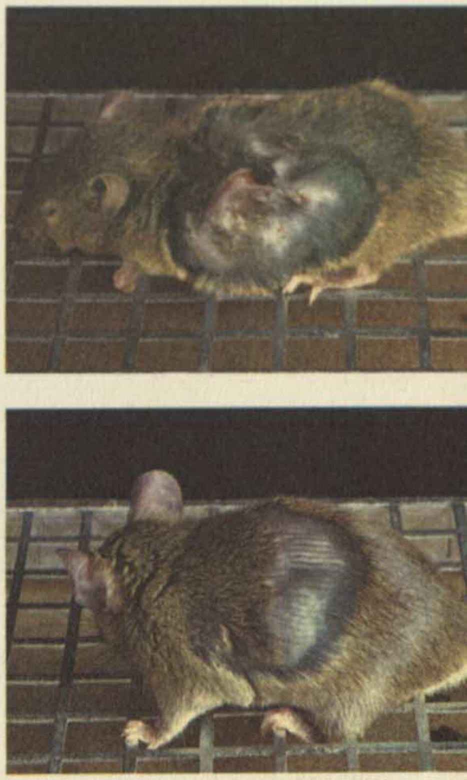
Hormonal disturbances

Another factor, which does not introduce any external element, can cause the appearance of a cancer, namely hormone disturbance.

If the ovaries of a female rat are removed and a fragment of one of these is placed in the spleen, the graft takes and secretes the hormone that is normally produced by the ovary. This hormone passes into the circulating blood. When the ovary is in its normal position, the secreted hormone reaches the pituitary gland situated at the base of the brain. The latter, acting as a regulator, stimulates the ovary to secrete this hormone whenever the quantity circulating in the blood reaching the pituitary is below its normal level. When the hormone is secreted by the graft in the spleen, it passes into the liver, which has the property of destroying the ovarian hormone contained in the blood that passes through it. The result is that the hormone does not pass into the circulation and does not reach the pituitary. Under these conditions and because of this barrier, the pituitary, not receiving any ovarian hormone, immediately stimulates the ovary to secrete. The latter, although abnormally placed in the spleen, receives these gonadotrophic stimuli and secretes more and more hormone, since none reaches the pituitary. Incited to excessive function in this way, the grafted ovary finally becomes the seat of a cancer.

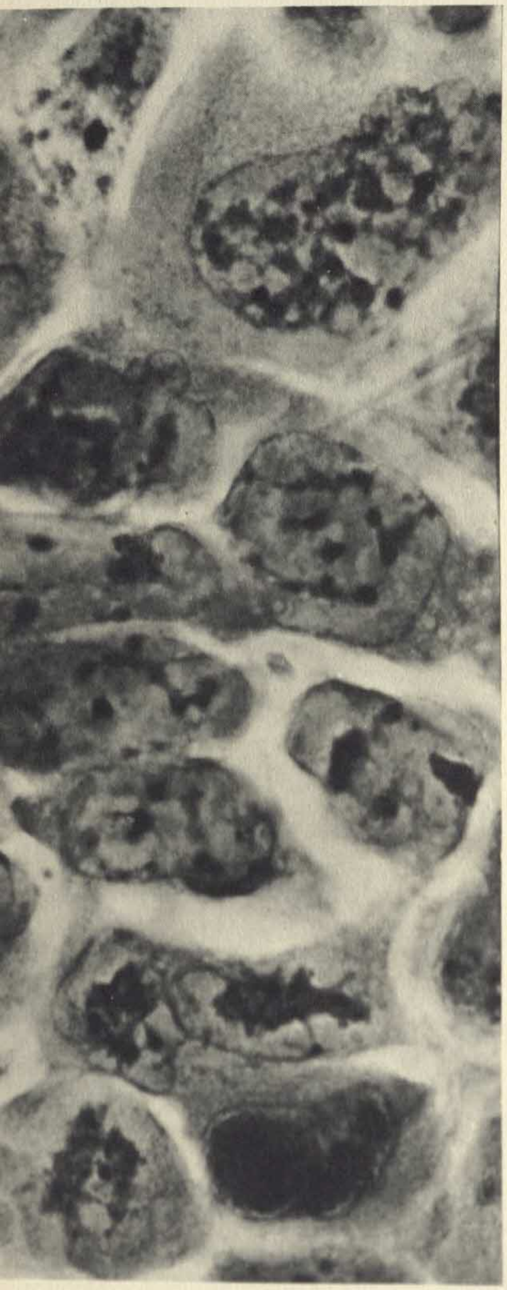
Numerous other types of experiments involve this principle of indirect hormonal derangement, leading to the appearance of cancers at different points in the system, always making use of the principle of hyperexcitation, as it were, *in vacuo*.

It can be seen how important this experiment is, since it demonstrates that cancer may appear in an organism without the introduction of any foreign material. It leads to the hypothesis that anything from outside that



These two photographs show the same mouse of a strain known as CBA. This mouse has been grafted with a sarcoma which appeared of its own accord on another mouse of the same strain. Above, ten days after the graft; below, fourteen days after the graft. By this time, cancerous ulcerations of the skin are already clearly visible. (Photo Lod, taken at Dr Kinsky's laboratory at the Hôpital St Antoine, Paris).

affects the nervous and endocrine systems—which are closely linked—may lead to the appearance of a cancer.



Culture of cells which have become cancerous through the action of a virus made up of DNA, which develops only in nuclei; note the deformation of some of the nuclei. (Photo Dr R. Robineaux).

It has been possible to demonstrate that some animals frightened by various means may, through nervous disturbance combined with possible secondary hormonal disturbance, end up by developing a cancer linked to this disturbance, itself caused by an adverse external factor. This result of psychological 'aggression' should lead us to study carefully the conditions in which certain cancers appear in man in relation to the conditions of modern life.

The role of viruses

Here the question is to what extent a virus can play a part in the phenomenon of cancer formation.

In man, we are not, as yet in possession of any information that would permit us to affirm the presence of a virus in any kind of cancer. At most, the possibility of its presence in certain cancers, such as leukaemias, has indirectly been suspected. Among animals, on the other hand, malignant lesions of viral origin have been found in chickens.

The existence of viral tumours was also proved in mammals, and at present one of the problems under discussion is the viral nature of a factor contained in the milk of certain strains of mice, which may be the operative factor in the production of mammary cancers where transmission might take place at the time of suckling. Furthermore, it has been possible to cause cancers in animals by injecting an extract of certain tumours, the filtrate of which does not contain any cells but probably does contain virus particles. Another remarkable fact is that these filtrates are capable of producing tumours of a different nature and even of causing them in different animal strains, compared with the original tumour in a given animal.

Although it is probable that in some cases a visible virus acts directly, in other cases, although it is not confirmed, it may be suspected because the virus may take on a 'masked' incomplete form made up of only part of its constituents. This form may not be identified, but it is often capable of finding in the cell those ingredients that enable it to reconstitute itself and to recover its carcinogenic activity.

It is interesting to note that the probable active element in this virus is also probably a nucleic acid, and that it can intervene in the nucleic acid system of the nucleus, nucleolus, or chromosome, as mentioned above.

This theoretical possibility, which has been confirmed by certain experiments with bacteria, has provided an argument for those who believe that the carcinogenic agents which we have reviewed here can, in fact, act on the cell only through a virus, revealed under the impact of such agents, thus providing the first essential stage before the appearance of cancer.

It seems, then, that although up to the present, in man at least, nothing allows us to claim that cancer is a uniform viral disease, the role of a virus in cancer cannot be rejected. Furthermore, in comparison with what has been observed in animals, it can be seen that several possibilities are open, and that these are not mutually exclusive. There may be cancers directly induced by viruses. Others may require a virus as the necessary intermediary between the carcinogenic agent and the cancer; or it may be possible that cancer can arise without the intervention of a virus. The relative probabilities of these three possibilities are still unknown.

In cases where a virus is present, we might hope to discover a more precise method of therapeutic approach by means of immunology; that is, through the body's defence reactions against virus action. This could lead us to envisage as a reasonable hypothesis the possibility of vaccination against certain cancers. This same hypothesis is admissible even in the absence of any virus, if the still doubtful proof of antigenic properties of certain cancers were to be established.

What is leukaemia?

Jean BERNARD

Leukaemia is a disease in which there is an excessive and disorganized function of the organs that produce white blood cells. It is probably akin to cancer, and the remarkable work of Oberling on chicken leukaemia clearly shows that the virus responsible for it may also give rise to neoplasms. Up to now, however, no such virus has been found in man, and this disease has not yielded up its secret. Nevertheless, with modern treatment, the course of the disease may be kept under control for a certain time.

Two kinds of white blood cells may be distinguished: polymorphonuclear and mononuclear cells. Polymorphonuclear cells have a many-lobed nucleus and a granulated protoplasm; depending on the colour of the granules resulting from staining, these are called neutrophil, eosinophil, or basophil cells. Mononuclear cells have a single nucleus and a cytoplasm that is generally devoid of granules; the most important of these are the lymphocytes.

Bone-marrow produces polymorphonuclear cells and the spleen and the lymph-nodes produce lymphocytes. This process goes through three stages:

1. The formation of primordial cells from which the lineages of blood cells are derived.
2. Maturation of these cells through successive stages;
3. Liberation of the mature cells which pass into the blood from the producing organs.

The suffix 'blast' designates primordial or immature cells; the suffix 'cyte' designates differentiated or mature cells. Thus the leukoblast is the cell that begins the lineage of white cells in general, and the myeloblast is the cell from which come those formed in the marrow, polymorphonuclear cells. A myelocyte is a cell in this same lineage of polymorphonuclear cells which is in the process of maturation.

In a healthy person, the organs that produce cells (bone-marrow, spleen, and glands) function regularly, harmoniously and vigorously. A triple equilibrium is maintained:

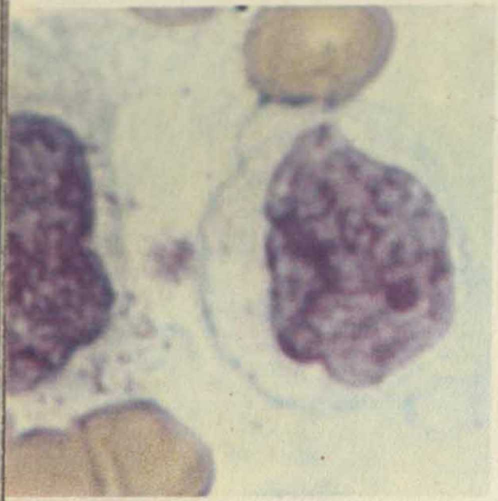
1. The number of white cells produced and passed into the blood is constant.
2. The relative proportion of the various types of white cells (polymorphonuclear cells and lymphocytes) is constant;
3. The cells passed into the blood are mature and fully differentiated.

Upsetting the balance

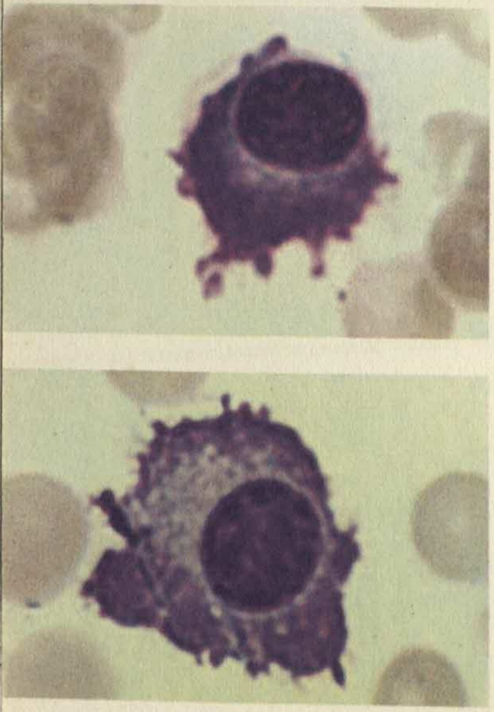
The term leukaemia is applied to those conditions in which this triple equilibrium is upset. Leukaemia is a disease defined by excessive, imperfect, anarchic, ectopic, and uniform functioning of the organs that form the white cells; *excessive*—these organs may produce fifty or a hundred times more cells than they do normally; *imperfect*—these cells are not fully differentiated, they do not mature; the earlier the cessation of differentiation, the more serious the leukaemia; *anarchic*—the formation of the cells is irregular, their nucleus and cytoplasm do not mature at the same rate, and the anomalies of these diseased cells are numerous; *ectopic*—not only the marrow, spleen, and glands, but the entire connective tissue becomes capable of forming white cells; *uniform*—this excessive proliferation is confined to a single type of white cell and all other types are eliminated.

A very grave disorder

Leukaemia is thus characterized by an extremely serious disorder of the organs producing white cells. The effect of this disorder on the blood is variable. Sometimes the malformed and immature white cells are put out



Monocytes typical of acute leukaemia (Photo Lod, see following photograph).



These cells (plasmocytes) are proliferating abnormally in a myeloma, another form of malignant haemopathy. (Photos by Lod, taken at the Blood Transfusion Centre of the Seine, director Dr André, with the collaboration of Dr Combrisson).

in enormous quantities in the blood; in certain exceptional cases the number of white cells is so high that the colour of the blood is partly changed. In the nineteenth century, cases of this type were the first to be recognized and this explains the origin of the word leukaemia, which means literally 'white blood'. Sometimes the number of white cells is normal or even diminished; leukaemia is characterized not by the state of the blood, but by the state of the organs that produce it.

This type of white-cell production in the producing organs has two consequences;

1. Hypertrophy of these organs.

2. The elimination of the other types of blood cells.

The two major symptoms of leukaemia are tumefaction of the white-cell producing organs, and insufficiency of blood.

Hypertrophy of the spleen and of the lymph nodes of the neck, armpits, and groin are easily recognized by observation, or at any rate by touch; hypertrophy of the deeper glands, especially those in the thorax, can be seen by radiography. Hypertrophy of the marrow, which is enclosed inside the bones, is indicated by pains in the limbs and sometimes by modifications of the skeleton detectable by X-rays. Blood insufficiency means that:

1. Red cell production is hindered, from which serious anaemia results, with the usual manifestations (pallor, breathlessness, and extreme fatigue).

2. The blood platelets (structures concerned with coagulation) are affected, leading to haemorrhage of the skin, viscera, and mucosa.

3. Normal white cells are affected, with consequent serious risk of secondary infection and fever.

These symptoms are associated in different ways in each patient; but they are useful in diagnosis. This, however, can only be confirmed by means of laboratory tests: blood-tests and sampling of the blood-forming organs by the technique of puncture. The examination of peripheral blood involves the enumeration of the different sorts of cells (in this way diagnosis can be made of anaemia; diminution in number of blood platelets; and an assessment of variation in the number of white cells, which may be greatly increased, slightly increased, normal, or even diminished); and a study is also made of stained slides of the various forms of white cells, their numerical proportions, and the presence or otherwise of abnormal cells.

The method of taking a puncture of the blood-forming organs has been known for thirty years. Puncture of the marrow, which is made in the sternum or iliac bone, and puncture of the lymphnodes present no difficulty and are current practices; the puncture of the spleen requires some precaution and necessitates immobilization of the patient for some twenty-four hours. By means of the puncture needle it is possible to take a small quantity of tissue from the marrow, spleen, or node. This tissue is then examined by the usual microscopical techniques. By this means it is possible to recognize fundamental disorders at their point of origin—excess of cell output, arrest of maturation, and malformation. The practice of making these organ punctures, which may be renewed during the development of the disease, has been the means of providing a firm diagnosis in leukaemia.

Three forms of leukaemia

The clinical picture and the development of leukaemias are related to the different white cells subject to abnormal proliferation. Three forms of leukaemia are of special importance:

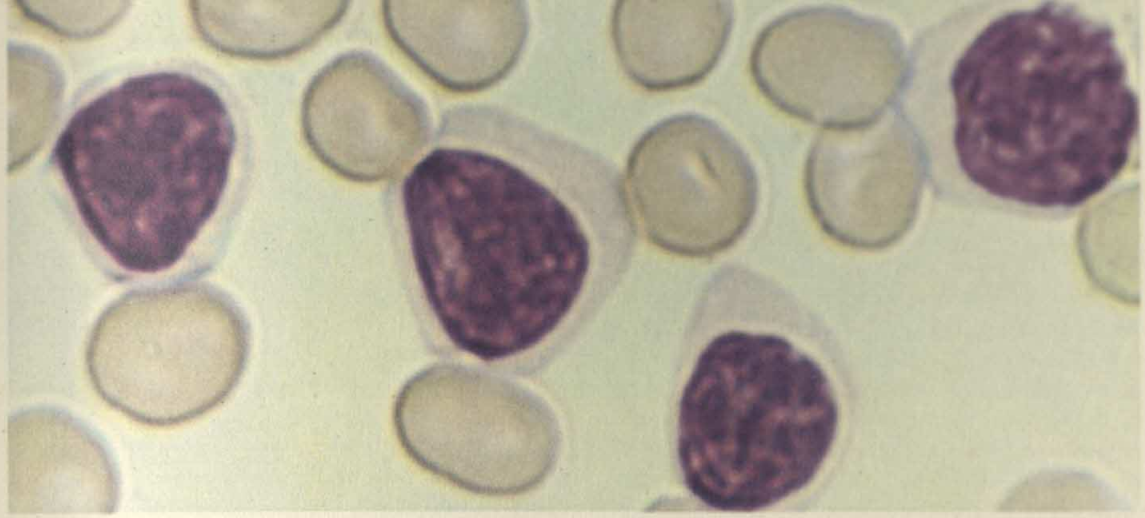
1. Chronic myeloid leukaemia (proliferation of imperfectly differentiated cells of the polymorphonuclear type—myelocytes).

2. Chronic lymphoid leukaemia (proliferation of the lymphocytes and their immature precursors).

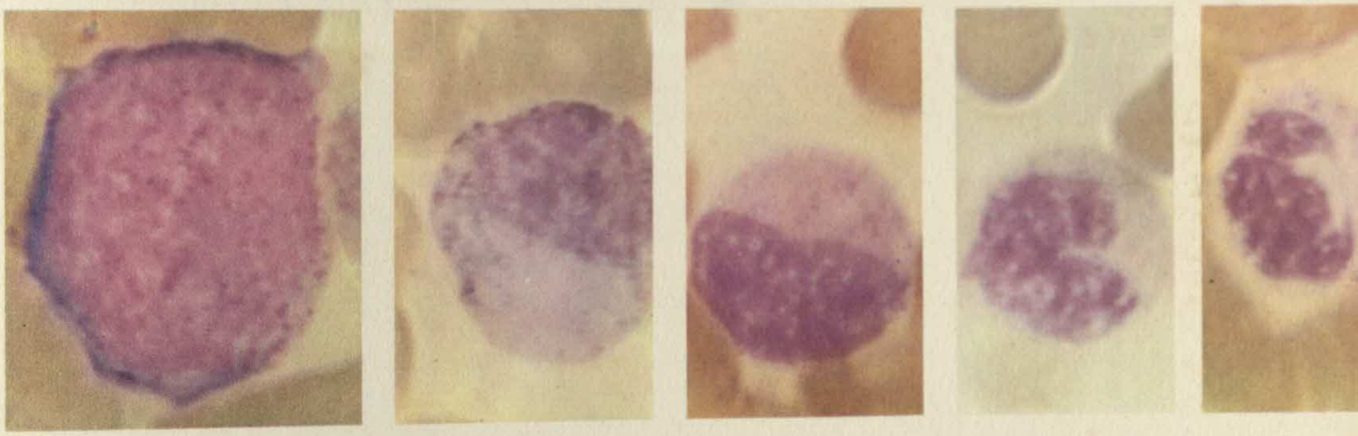
3. Acute leukaemia, (proliferation of immature primordial cells or those that have just begun to differentiate—the leucoblasts).

Chronic myeloid leukaemia occurs at all ages, but particularly in adults during middle age. The two main symptoms are a considerable increase in the size of the spleen and a considerable increase in the number of white cells (which, for example, increase from 6,000 per cubic millimetre, the normal figure, to 300,000), with the passage into the blood of immature cells or myelocytes.

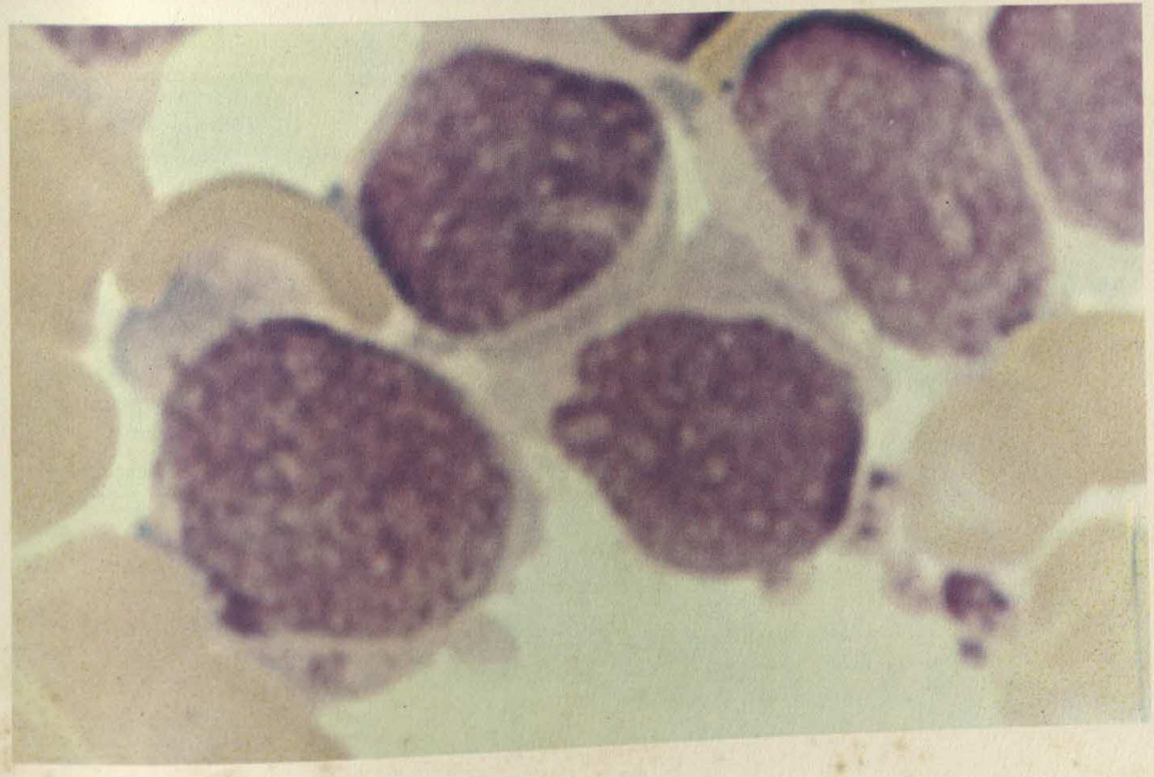
Chronic lymphoid leukaemia occurs in adults, especially old people. Enlarged glands deform the neck, armpits and groin. Increase in size of the spleen is moderate. Skin lesions are possible; the number of white cells is often moderately increased, sometimes very much increased, and sometimes normal. The normal equilibrium of the various types of white cell is upset. The lymphocytes predominate; their level in the blood rises from a normal value of between 30 per cent and 35 per cent to 60 per cent, 80 per cent, or 100 per cent; their level in marrow smears ranges from 0 per cent to 5 per cent (normal value) to 40 per cent, 60 per cent or 100 per cent.



Blood smear from a patient suffering from chronic lymphocytic leukaemia. The chromatin of the nucleus appears in the form of irregular clumps, the cytoplasm is without granules.



From left to right, normal differentiation of polymorphonuclear white cells, starting with the myeloblast. In chronic leukaemia one of the 'white' series proliferates (lymphoid or myeloid condition), invades the entire marrow and inhibits the normal production of the other series; this process is shown here. In acute leukaemias, on the other hand, abnormal proliferation takes place in the immature primordial cells, and the differentiation shown is abnormal.



Bone-marrow smear of a patient suffering from myeloblast leukaemia. Myeloblasts in the marrow are large parent cells that develop into granular leucocytes (one of the forms of circulating white cells).

Acute leukaemia occurs at all ages, but attacks young children with cruel frequency. The main symptoms are pallor, as a result of anaemia, bone pain, haemorrhages, and fever. Sometimes these symptoms are grouped and allow of an easy diagnosis, sometimes they are dissociated and at first only slight, and therefore misleading. A diminution in the number of red cells and platelets is usual. The quantity of white cells in the blood is variable. Their number may be increased, normal, or even diminished; diagnosis is confirmed by sternal puncture. The very variable normal tissue of the bone marrow is replaced by a uniform covering of primordial cells of the white lineages, or leucoblasts.

Leukaemia develops spontaneously and progressively, and whether regular or irregular, is irreversible and fatal. Its duration is very variable. Certain acute leukaemias kill in a few weeks, others in a few days. Certain chronic leukaemias allow survival for ten, fifteen, or even twenty years.

Two types of treatment

Treatment is capable of partly modifying the development of the disease and is of two types: destructive and regulatory. The former aims at destroying the leukaemia tissue and includes the use of:

1. Radiation (X-rays, and radio-active cobalt, or phosphorus) which for a long time has been the only practical means of treating leukaemia.

2. Certain chemical substances, called cytostatics because of their effect on cell division or mitosis. (To this class belong certain nitrogenous mustard-gas derivatives and sulphonic esters used in the treatment of the two main types of chronic leukaemia.)

3. Other preparations, called antimetabolites, which disturb the metabolism and functioning of the leukaemic cells. These antimetabolites are employed especially in the treatment of acute leukaemia.

Regulatory methods of treatment are designed to correct the fundamental disturbance of cell output. These methods are still far from achieving their aim, but they hold great promise for the future. This type of treatment includes exchange transfusion of blood, a method by which, in 1947, the treatment of acute leukaemia began; and the use of pituitary and suprarenal hormones (cortisone and derivatives) which are widely used today in the treatment of the various types of leukaemia.

The effect of these treatments is threefold: they considerably increase the comfort of the patients; they induce remissions, that is to say, the disappearance of all clinical and biological leukaemia disorders; and during remission, the leukaemia person leads an absolutely normal life. In certain cases these treatments notably prolong the patient's life.

At present, the progress of therapeutic research is encouraging. It is reasonable to anticipate an improvement in the situation in the not too distant future. Progress would be even more rapid if the causes of leukaemia were known; on this we only possess fragmentary data derived from the study of human and animal leukaemia.

Benzene and radiation leukaemia

There are two leukaemias in man of which the causes are known; benzene and radiation. Benzene, or more correctly, the impure products based on benzene called benzols, are used in a number of different industries (rubber adhesives, colour printing, paints, the manufacture of artificial flowers, and of mirrors). These benzols are capable of destroying bone-marrow cells; more rarely they may cause leukaemia. Benzene leukaemias may occur in workers who have been in contact with toxic vapours for ten or fifteen years. It may only appear several years after exposure to the danger has ceased. The limitation of the use of benzene in industry has fortunately diminished the number of blood disorders caused by this substance.

Much more worrying are leukaemias caused by radiation, or radioleucoses. They first became known among radiologists; several pioneers of radiology died of leukaemia after fifteen or twenty years' exposure to X-rays; forewarned, modern radiologists are usually properly protected, but leukaemias still occur among doctors and nurses who work with cases where protection cannot be ensured (the passage of catheters into cardiac cavities and surgery without a screen). Physicists who handle radioactive substances may also be victims of leukaemia and some of the most famous have died in this way.

A second stage in our knowledge of radioleukaemias was reached after the explosion of atom bombs on Japanese cities. The proportion of leukaemia sufferers among the survivors was seven times greater than in inhabitants of other Japanese towns. This frequency increases in proportion to the proximity of the victims to the point of explosion; it did not reach its maximum until four or five years after the fall of the bomb. More recently, certain leukaemias have been attributed to radiation treatment (for example, radiotherapy for vertebral rheumatism), to the application of radio-isotopes, and even to certain radiological examinations. Leukaemia has appeared in young infants exposed to radiation during intra-uterine existence through radiological examinations of their mothers. The interpretation of these facts is still the subject of verification and discussion. In no case should fear of a rare and hypothetical leukaemia cause the postponement of a useful radiological examination; conversely, this fear forbids unnecessary radiological examinations.

Generally speaking, the importance of these radio-leukaemias is great. They have been described as occurring both in man and animals, and provide definite proof of the role of an external factor. At the same time, they show that this external factor is not the only one, since leukaemia attacks only some of the doctors who are exposed, nor did it attack all those who were bombed in Japan.

Radiation may perhaps partly explain the increasing frequency of human leukaemias. While the general frequency of cancers is more or less stabilized (except for lung cancer, which is increasing), the number of leukaemias continues to grow. The same increase has been reported in all continents; leukaemias attack all peoples and all races, although chronic lymphoid leukaemia is practically unknown in China and Japan. Other data supplied by the study of human leukaemia are negative. There is no contagion. There is no clear hereditary factor or family predisposition, despite certain dramatic exceptions. The children of a leukaemic father or mother are born, and remain, normal.

Animal leukaemias

Leukaemias have been reported in numerous animal species, ranging from invertebrates to cattle and dogs. Two animal leukaemias have, however, a particular importance: chicken and mouse leukaemia.

The study of chicken leukaemia reveals three facts of importance:

1. It provides an example of a disease that is more varied than in human beings, affecting red as well as white blood cells. The analogous variety of leukaemia affecting red cells is known as avian erythroblastosis.

2. It supplies the first known example of leukaemia caused by a virus. The virus may be observed and photographed under the electron microscope, cultivated in special media, and transmitted from chicken to chicken or to chick embryo.

3. It has supplied a precise and strong argument in favour of the old, rather vague, hypothesis which, for a long time, linked leukaemia with cancer (the old term 'blood cancer' was used for many years). The virus of chicken leukaemia, placed in special physio-chemical conditions, becomes capable of causing cancer. It can then be modified again, and again cause leukaemia.

Experimental leukaemia laboratories use two sorts of mice, ordinary mice of uncertain pedigree, but chiefly genetically pure strains of mice whose pedigree has been recorded for dozens of generations. There are three kinds of leukaemia in mice:

1. Spontaneous leukaemias, which are fairly close to human leukaemias, appearing with given frequency in a given strain.

2. Transplanted leukaemias, grafted from a leukaemic mouse to a non-leukaemic mouse susceptible to leukaemia.

3. Leukaemias induced by radiation or by certain chemical substances derived from tars.

Research during the last few years has established that viruses play a part in the origin of some mouse leukaemias. A baby mouse, a few hours old, can become leukaemic following concentrated injections of viruses. A mouse leukaemia due to a virus may be transmitted from mouse to mouse. The fundamental constituents of these viruses, that is to say, the nucleic acids of the virus, may, in certain cases, cause leukaemia.

Recent research, both in animals and man, is aimed in two main directions—on the one hand, applying the most recent data of molecular biology, towards the discovery of a difference between the molecular constitution of the leukaemic cell and that of the normal cell; for this purpose very refined techniques are used (such as the electron microscope, biochemistry, and immuno-chemistry): proof of this difference would have very important therapeutic consequences; at the same time, research workers are trying to identify the specific hormonal factors and extra-cellular factors known as the environment of leukaemic cells, which favour the development of these cells. This study, stimulated by the effects of exchange transfusion, and by the goal of complete remission, may also open the way to effective therapeutic progress.

HISTORICAL NOTES

The study of cells
18th century
First description of blood cells under the microscope by LEEUWENHOEK.

1929
First sternal puncture by Arinkine.

1950
Application of the phase-contrast microscope and the electron microscope to the study of leukaemic cells.

Description of leukaemias
1841
DONNE: *First description of leukaemias.*

1847-1850
VIRCHOW, BENNET: *First description of the two chronic leukaemias.*

1890-1900
FRAENKEL, EBSTEIN: *First description of acute leukaemias.*
Treatment of leukaemias
1863
Arsenic, the first treatment of chronic leukaemia.
1900-1905
First radiation treatment of chronic leukaemia.

1945-1955
Chemotherapy experiments.

1947
First treatment of acute leukaemias (exchange transfusion).

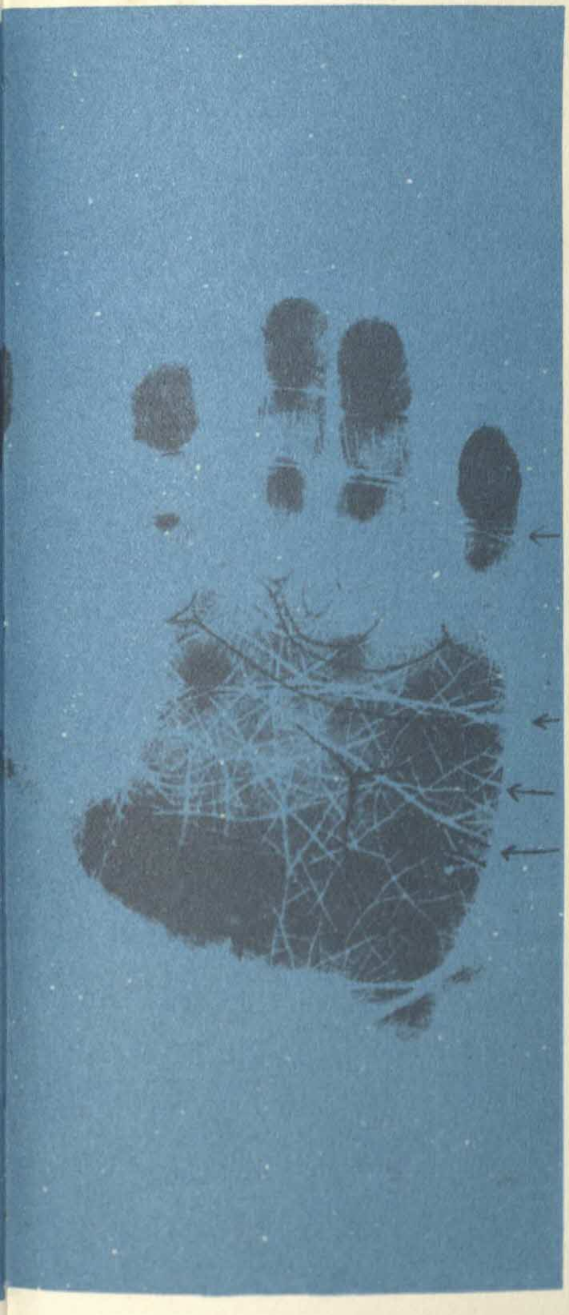
1950
Introduction of hormones (cortisone) in the treatment of leukaemias.

PART FOUR

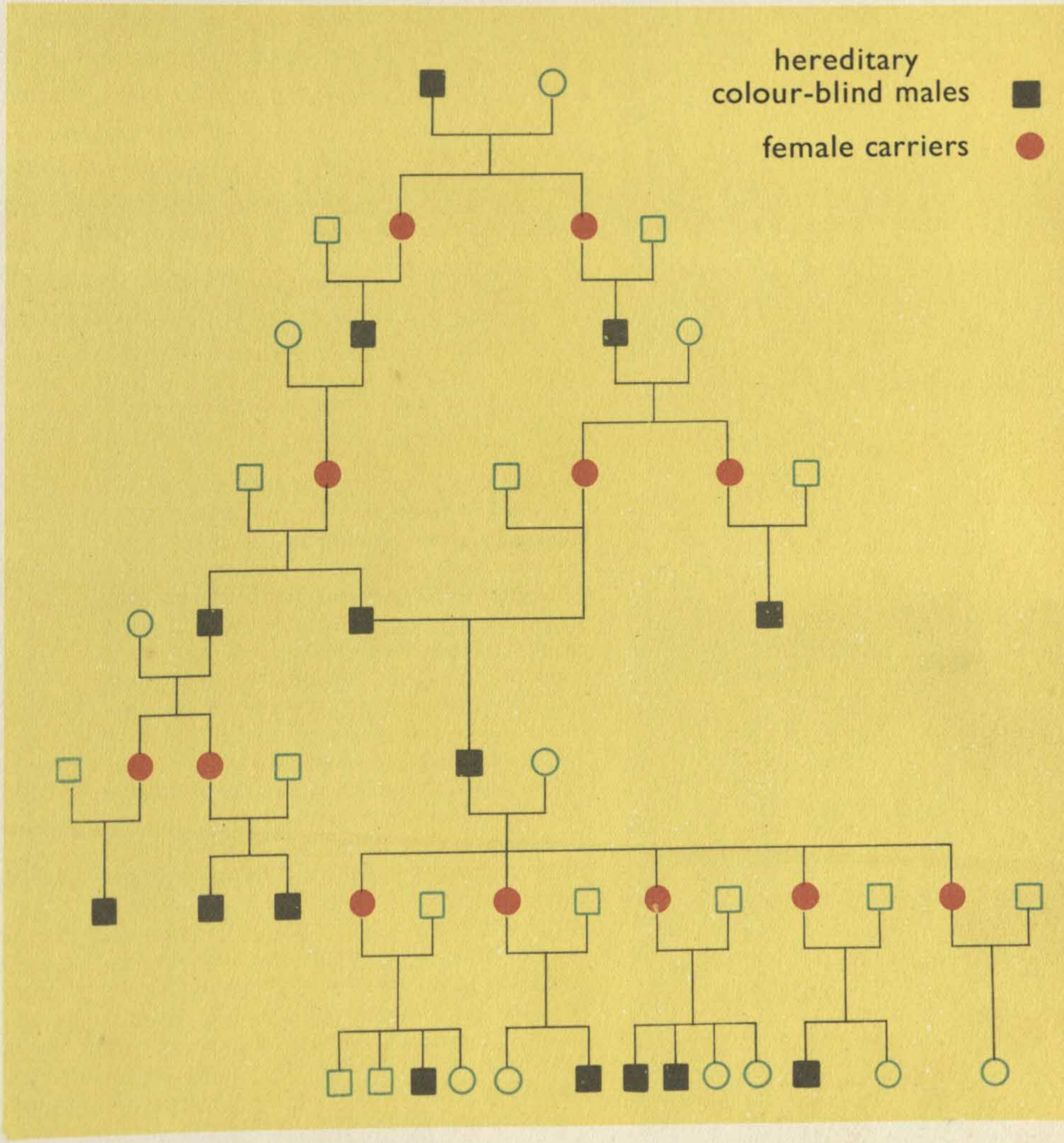
Hereditary diseases

Certain disorders affect not only one organ or one tissue, but the whole body. These are generally congenital conditions which are transmitted from the parents to their children at the same time as the specific characters borne on the chromosomes. Nevertheless, geneticists still try to determine the probability of the appearance of abnormalities in each generation by drawing family trees based on the dominant or recessive characters of the parents and the application of Mendel's laws. (Above,

Chromosomal diseases



Psychological diseases



right). Mongolism is a well-known example of a disease which is not strictly speaking hereditary, but which is linked with a 'chromosomal abnormality'. This disease has marked effects on the physical and mental development of a child afflicted by it, though there may be no sign of it in the parents. Above, we see one of the striking signs of mongolism, the abnormal distribution of the lines of the hand of a mongol boy (right), as compared with the normal one shown by his mother's palm (left). One other type of disturbance, psychological disease, affects the whole individual. This remains the stumbling block of modern medicine, for the treatment of psychological diseases implies a complex analysis of causes, both affective and social, and for this we need a detailed knowledge of the psychological mechanisms which we do not yet possess.

Heredity

Maurice LAMY

For a long time, nothing was known about the laws of heredity, but the extraordinary advances made in genetics during the past thirty years have shown this to be a fundamentally important branch of science. It is the study of those phenomena which are essential for the transmission of life itself and the constitution of every living being. It has given medicine a basis for the understanding of hereditary diseases by classifying them and so enabling them to be distinguished from apparently similar diseases which are acquired. Also, through the direct study of the chromosomes in man, it has enabled us to understand the occurrence of certain congenital abnormalities.

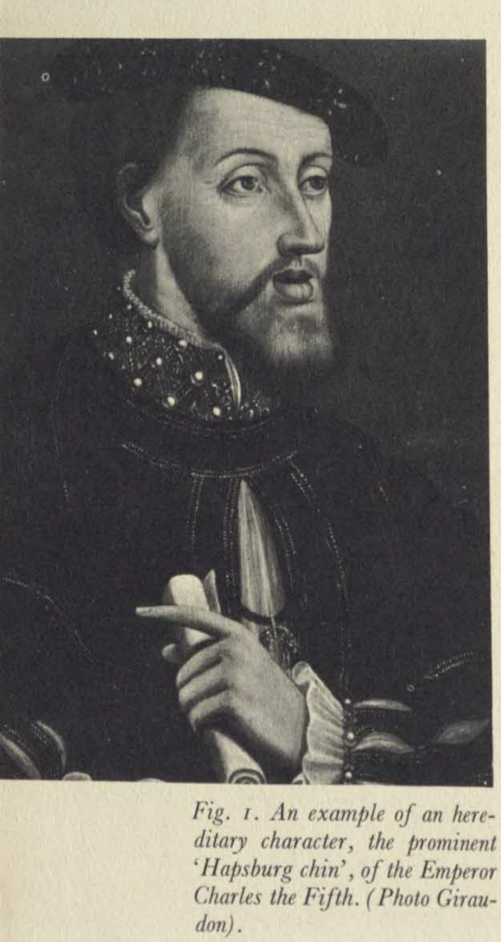


Fig. 1. An example of an hereditary character, the prominent 'Hapsburg chin', of the Emperor Charles the Fifth. (Photo Giraudon).

What is heredity? According to the Oxford Dictionary it is 'the property in virtue of which offspring inherit the nature and characteristics of parents and ancestors; the tendency of like to beget like'. For a very long time no progress was made in this field. Until quite recently, some believed in the transmission of acquired characters and that both the appearance of new species and the phenomenon of evolution were to be 'explained' on this basis. We now know that this is not so. It has been realized since the time of Darwin that the external environment does not create new species but imposes a selection which allows the survival of those variants in a population that are better adapted to their conditions of life.

It is now universally accepted that the heritable variations which organisms show are the result of mutations and recombinations of genes, which lead to the production of some new character. Selection then acts on this character either to eliminate it or to allow it to be transmitted to ensuing generations.

The laws which govern heredity and account for the differences and resemblances between the generations were for a long time unknown. Although foreshadowed by some investigators, such as Augustin Sageret and Charles Naudin, they were only discovered in 1865, by an Augustinian monk, Gregor Mendel. Working with peas in the garden of his convent at Brünn, he worked out and described in a paper (which remained unknown for many years) the fundamental principles of heredity in the crossing of plants.

Since the beginning of this century, the science of heredity has progressed rapidly. Lucien Cuénot and William Bateson showed that the laws established by Mendel were valid not only for plants but also for animals, including man, and are in fact general laws. W. S. Sutton showed that the chromosomes, the active part of the nucleus of the cell, are the physical carriers of heredity. Thomas Hunt Morgan and his collaborators carried out epoch-making researches on *Drosophila*, a small fly which is easily and quickly bred, and showed that the factors of heredity or genes are strung out in linear order along the chromosomes. C. D. Darlington has demonstrated the structure and mechanism of the chromosomes in great detail.

Let us examine separately the transmission of unifactorial and of multifactorial characters, since the former is simpler than the latter. Unifactorial hereditary characters may be either dominant or recessive. We shall see what happens in each case.

Dominant and recessive characters

Let us first take an example of a dominant character, It may be 'Hapsburg chin'; an A or a B blood-group; woolly hair, or a white forelock in men; dark eye-colour; an abnormal shortening of the fingers, known as brachydactyly; night-blindness; haemophilia (persistent bleeding); or alcoholic jaundice. As will have been noticed, many of these characters are pathological. In this type of inheritance the person is a carrier of a gene responsible for the anomaly in question, the gene being situated on one chromosome of a certain pair of chromosomes. In the corresponding place on the other chromosome of the pair is a normal gene. Under the conditions we are considering here, the mutant gene, by the very fact of its presence on one of the chromosomes, leads to the appearance of the character concerned. It dominates the normal gene, called the normal allele, and the character that it controls is therefore called 'dominant'. The mechanism of the reduction-division at the time when the germ cells are formed, and the recombination of genes at the moment of fertilization, as shown in the diagram (fig. 2) explains why, if one of the parents is a carrier of the mutant gene and is affected by it and the other is normal, half the offspring will be affected and the other half normal.

A character is called dominant if it is always transmitted to the descendants, even if in the parent the gene that controls it is present in the heterozygote state (that is to say, when the corresponding genes on the two chromosomes are not the same). If the individual has two similar genes, he is a homozygote. In the case we are dealing with, that of a heterozygote carrying a dominant gene, this gene is passed on to the descendants even if the partner is homozygous for the normal gene.

If the character in question is recessive, however, things happen differently. In the case, for example, of blue or grey eyes, or blood-group O, or albinism (the absence of the normal pigment in the skin, the eye, and the hair) or deaf-mutism, a union which gives rise to a person exhibiting one of these characters is between two individuals who are both heterozygotes for the gene in question. The character is recessive; that is to say, the gene responsible for it is dominated by the corresponding normal gene and cannot express its effects when there is such a normal gene at the corresponding point on the other chromosome of the pair. For the character to show up, it is necessary that the subject has received the gene from both his mother and his father, so that he is homozygous for the gene in question. The diagram (fig. 3) shows why the two parents who are heterozygous for the condition appear to be normal, and also why, on average, only one in four of their children will be affected. This one, by chance, will have received the mutant gene from each of his parents and so is homozygous for it.

It can easily be seen that in the case of the transmission of a dominant character it is easy to pick out the hereditary nature of the condition because it is transmitted directly from the parents to the children. But in the case of a recessive character the hereditary nature is much less obvious because in most cases the affected person is the offspring of normal parents.

Some hereditary diseases are transmitted by what is called 'sex-linked' transmission. Twenty-two of the pairs of chromosomes which are found in man, out of the total of twenty-three pairs, are called autosomic and play no part in the determination of sex; the last, or twenty-third, pair are called the sex chromosomes, because they play the principal part in the determination of sex. A woman has two X chromosomes; a man has one, and one Y chromosome, which is smaller. Certain diseases, like the defect of blood coagulation called haemophilia, and some forms of colour-blindness, are due to the presence of a defective gene on the X chromosome, or more exactly, on that part of the X chromosome which does not correspond to the Y chromosome and which is therefore found only in the two chromosomes of the female. As shown in the diagram (fig. 3; see also the family tree on p. 137), the union which gives rise to a haemophiliac, or to a colour-blind person of this type, is between a normal man and a woman who is a heterozygote for the responsible gene, in other words, a 'carrier' of the gene. The mechanism of reduction-division, fertilization and recombination results in a family in which only the males are affected, and, on average, only half of them. The females are protected because on the normal X chromosome they possess a normal gene which 'dominates' the mutant gene with pathological effects and prevents its expression.

The facts dealt with so far have been expressed diagrammatically to make them easier to understand, but in reality they are more complex. For example, as well as the simple cases of dominant and recessive inheritance, we have to account for cases of an intermediate type. That is to say, there are genes that produce characters which are neither dominant nor recessive but intermediate, such as red hair, or sickle-celled anaemia. A person who is heterozygous for a particular mutant gene may be less affected than one who is

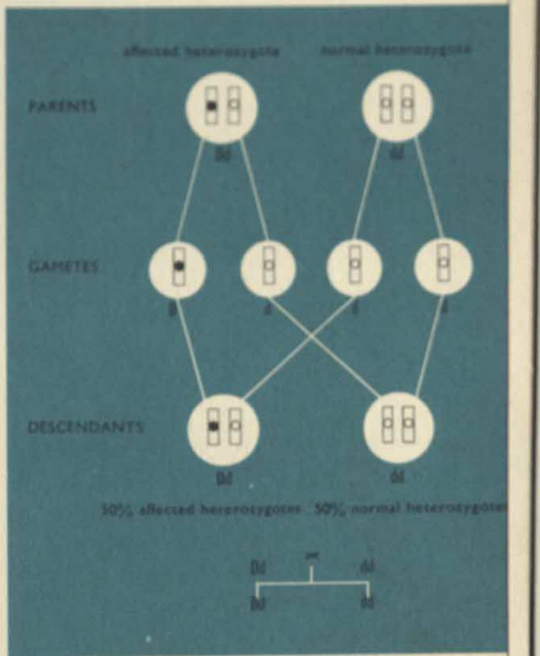


Fig. 2. Crossing between two subjects one of whom is a heterozygote for a gene producing a dominant character (Dd) and the other normal (dd). Half of their descendants will be normal and half affected.

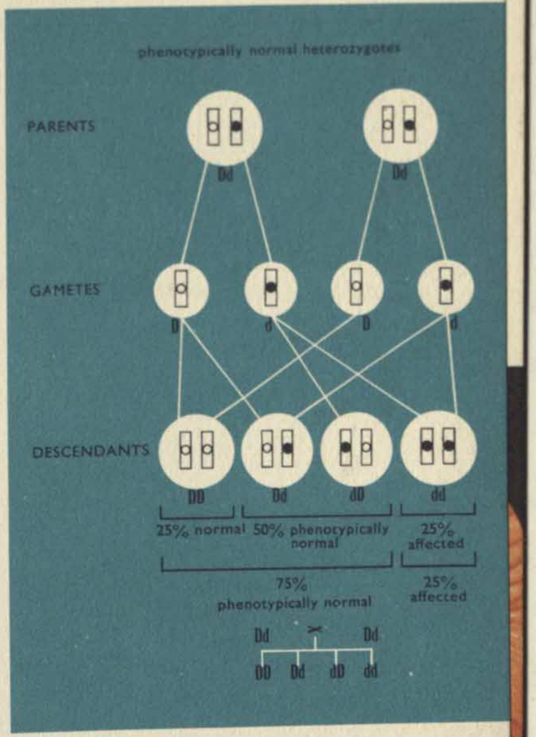


Fig. 3. Crossing between two subjects who are both heterozygotes for a gene producing a recessive character (Dd). According to the laws of genetics, three-quarters of the descendants have a normal appearance, (phenotypically normal), and one quarter are affected.

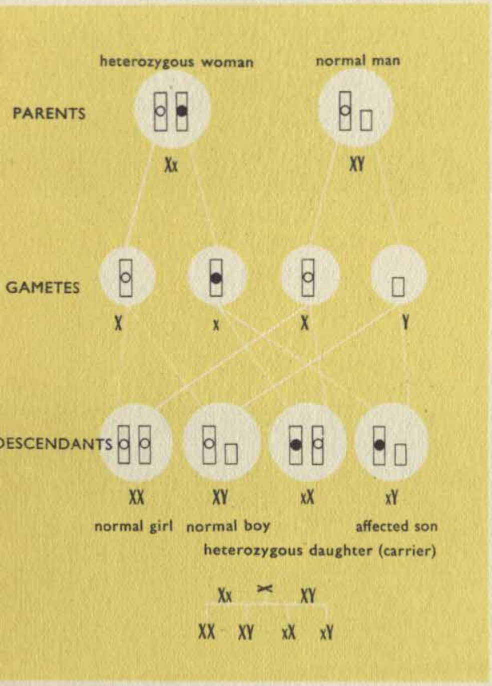


Fig. 4. Crossing between a woman who is a heterozygote for a gene producing a recessive character carried on the X chromosome (Xx), and a normal man (XY). Half of their descendants will be normal. Among the half who carry the mutant gene, the daughters (xX) will be carriers, and the sons (xY) will be affected. This is what happens in certain hereditary diseases, such as haemophilia. (Figs. 2, 3 and 4 from 'L'hérédité, éléments fondamentaux de génetique' by Maurice Lamy, Horizons médicaux, *1957–58; Nos. 45 to 54, Laboratoire de l'Hépatrol).*

homozygous for that gene; whereas someone who is homozygous for the normal gene will of course be unaffected. In the heterozygote it may be possible to show the presence of the milder diseases, either by careful examination or through various laboratory tests.

One other aspect of hereditary diseases or afflictions must be mentioned. It is not always a question of a malformation of one organ or tissue: sometimes the effect is one of function, an abnormality of metabolism, or of the physiological exchanges. Such affections as diabetes, gout and others which are rarer and which come under the general heading of malfunction of various glands of internal secretion, are of this type.

Multifactorial transmission

Other characters are transmitted by less simple means. They are not under the control of one single gene, but of several, and such characters are therefore sometimes said to be subject to 'multifactorial transmission'. Many so-called 'normal' characters, such as height, weight, intelligence, and traits of individual character are not due to the possession of any single gene or factor, but to the summated effects of several genes, each of which, however, conforms to the principles of Mendel's laws. We can thus explain the diversity of such characters among the offspring of a particular couple and the presence of individuals, whose features and peculiarities show resemblances to those of both parents.

Furthermore, as Sir Ronald Fisher showed, the effects of a gene are also conditioned by other genes of the gene-complex of an organism. In addition, most hereditary characteristics are also influenced by the environment in which the individual lives and has lived. It is fairly obvious that weight depends to some extent on the adequacy or inadequacy of diet. Someone who is well nourished and has been brought up under favourable conditions will probably be taller than someone who has not. And of course the pigmentation of the skin will vary according to exposure to the sun's rays.

It is the same with hereditary diseases. Certain diseases which unquestionably have a hereditary basis (for example, diabetes, gout, perhaps certain cirrhoses and possibly even tuberculosis) are nevertheless dependent to a great extent on environment. Excessive eating and drinking, poor hygiene, and contact with a pathogenic organism, may give the hereditary tendency a chance to express itself. The same thing can be said of certain psychopathologies, that is to say, certain mental defects.

There are methods which allow us to estimate the respective roles of heredity and environment. One of these is the comparison of twins. It is well known that there are two types of twins. One is the dizygotic, in which two ova have been fertilized by two sperms, resulting in ordinary brothers or sisters who happen to be of the same age. The other type, monozygotic twins, come from one egg which has been fertilized by one sperm. The fertilized ovum divides into two halves, which give rise to separate individuals. These are, from their origin, really two halves of the same individual and are genetically identical. Comparison of such twins can obviously give us some idea of the relative effects of heredity and environment. The resemblances between them are clearly due to heredity, but the differences must be due to environment.

It is not necessary to stress the importance of hereditary diseases nowadays, nor of the part they play among diseases in general. Man is progressively eliminating the effects of his old enemy, infection. As a result, the role of heredity is becoming more important. It would be a great mistake to think that the study of heredity has only a theoretical importance and is of no practical value. Of course, the fact that a disease is of hereditary origin does not prevent it from being treated. Diabetes can be, if not cured, certainly controlled by the use of insulin. Haemophilia is treated by transfusions, and haemolytic jaundice by removal of the spleen. But prevention is better than cure. One of the main tasks of the medicine of the future is the prevention of hereditary diseases.

Apart from moral arguments, it will be seen from what has been said that it is impossible to prevent the transmission of hereditary diseases by the sterilization of affected persons or carriers. Nevertheless, our understanding of the precise method of transmission of some of the hereditary diseases, whether they be dominant, recessive, or sex-linked characters, enables us to predict the possible results of certain unions and, if it appears necessary, to advise against them. In the future, when we have made more progress towards understanding and detecting heterozygotes, it will be possible to be more precise in giving such advice. In any case, certain marriages between persons who are closely related should be advised against, since there is more likelihood of their both possessing the same mutant genes controlling recessive and undesirable characters.

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(1) *For more information on the subject of genes and the 'chromosomal mechanism', see the chapter on 'Problems of Heredity', in Volume 1, The Living Universe; the chapter on 'Mongolism', in this volume, and E. B. Ford:* Genetics for Medical Students, *Methuen, London, 1956.*

Abnormalities of vision

A. FRANCESCHETTI and A. MENESTRIER

It is impossible to discuss all types of ocular abnormality in a few pages. As examples, we have therefore chosen some of the more frequent and more important affecting children, of which only the essential outlines will be given.

Squinting in infants

The visual axes are theoretically parallel when a person is looking into infinity with the head straight and the eyes fixed on an object at the same height as the line of vision. The macula being slightly eccentric in relation to the posterior geometrical pole of the eye, the visual axis[1] and the optical axis[2] normally form an angle, called alpha. As a result, an eye which is fixing an object sometimes appears not to be looking straight at it, and the corneal reflex[3] seen when a beam of light is focused on the cornea in a dark room, which should theoretically be in the geometrical centre of the cornea, is often a little on the inner side of it. This could suggest that there is an outward deviation of the visual axes, which does not really exist; this can be worrying to the family, and even to the ophthalmologist, if the child is very young.

A deviation of the visual axes can remain latent and only be shown by certain tests, of which the simplest is the occlusion test.[4] A condition of latency is that there shall be good binocular vision.[5] Difficulty with this can lead to the appearance of a real deviation of the visual axes which was already latent; this is called a strabismus or *tropia*, otherwise known as a squint. A latent deviation is called a *phoria*. The deviation of the visual axes can be horizontal, or vertical, or both at the same time, in which case the squint is mixed, or oblique. Horizontal deviation can take one of two forms. If the visual axis is turned inwards, the squint is convergent (fig. 6); if it is turned outwards, the squint is divergent (fig. 7). The deviation, whether horizontal or vertical, can either be fixed in the same eye, giving a unilateral or monocular squint, or it can affect both eyes in turn, giving an alternating squint (fig. 8).

The disturbance of binocular vision which follows deviation of the visual axes can take one of three forms:

1. One of the two images is neglected and not perceived; this is *suppression*.
2. This suppression of the image in a squinting eye can become permanent, with the result that the visual acuity of the eye is much reduced, even though it is anatomically normal. Such an eye is called *amblyopic*. This happens most often in the case of monocular squints.
3. When a squint has existed for a long time without treatment, points of the two retinas which in fact do not normally correspond may become corresponding. If such correspondence (called abnormal correspondence[6]) persists after an operation to correct the deviation, it can lead to post-operative diplopia[7] a complication found most often in children operated on after the age of ten.

The chief predisposing causes of difficulty with binocular vision are errors of refraction, such as myopia or hypermetropia,[8] anisometria, and anisoconia.[9] The causes of deviation of the visual axes are abnormalities in the shape of the eye sockets or of the extrinsic muscles that rotate the eyeball, or defects in the innervation of these muscles. Errors of refraction may be a direct cause of a squint, especially if there is a gross error in one eye. Paralytic squint may result from injury to the brain or orbits or from neurological disease. In abnormalities of the eye sockets or of the upper part of the face, or of the muscles themselves, the squint is usually congenital, or appears very early in life.

Divergent squint often appears to be inherited directly, but in convergent squint it seems that it is the predisposing factors which are inherited rather than the squint itself. But since the real importance of each of these factors is difficult to determine, the laws governing the inheritance of this form of squint are still not clearly understood.

Once the presence of a squint has been suspected, measures to cure it should be sought. A squint, if treated early and successfully, should not only appear straight, but should result in binocular vision. When the angle of a squint is so great that fusion of the

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(1) *The visual axis AB is the straight line joining the macula to the point of fixation, the macula being that area of the retina in which vision is maximal.*

(2) *The optical axis A′B′ joins the posterior geometrical pole of the eye to the geometrical centre of the cornea.*

(3) Corneal reflex *is the image formed by the reflection of a point of light on the cornea.*

(4) *In the* occlusion test *the patient fixes his gaze on a light source and then covers one eye. The latent squint becomes evident behind the cover and is revealed when the observer quickly removes it.*

(5) Binocular vision *results from the co-ordination of the two eyes, which is normally so perfect that they appear to work as one.*

(6) *Retinal correspondence is said to be abnormal when it is no longer between the two maculae, but is between the macula of the fixating eye and a point on the retina away from this in the squinting eye.*

(7) Diplopia *is the impression of seeing two objects where in fact there is only one.*

(8) *The eye is an optical apparatus consisting of refractive media separated by curved surfaces the shapes of which are portions of spheres. An image of external objects is formed on the retina where the sensory elements are situated. In* myopia *(short sight) the image is formed in front of the retina; in* hyermetropia *(long sight) it is formed behind it.*

(9) Anisometropia *consists of a fairly marked difference between the refractive errors of the two eyes, or between a normal and an abnormal eye. This leads to a difference in the sizes of the images seen by each eye* (anisoconia). *Anisoconia can also occur without anisometropia, it is then called primary anisoconia.*

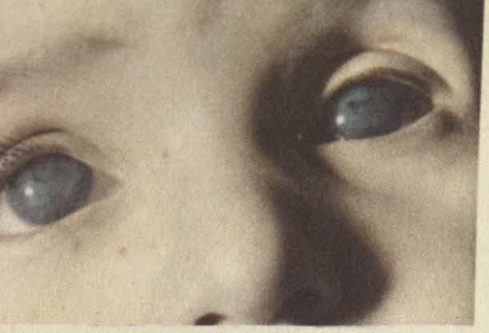

Fig. 1. Bilateral buphthalmia (infantile glaucoma), showing the large diameter of the cornea and its slightly hazy surface. (Photo Dr Ménestrier).

two images is impossible, an operation must be performed. This can be done even in the case of a child of less than a year old. The operation may be carried out in more than one stage; the external ocular muscles are removed and reattached to the eyeball so that the eyes appear straight and fusion of the image is possible. Errors of refraction are corrected both before and after the operation. Glasses can be worn from the age of six months and orthoptic exercises to strengthen the binocular vision can be practised from about the age of three. If steps are taken as early as possible, they will to a considerable extent prevent the disturbance of binocular vision and—even more important—amblyopia, the most serious result of a persistent squint.

Congenital glaucoma in children

Glaucoma is an ocular condition characterized by a rise in intraocular tension[10] which results in damage to the tissues of the eye and in consequence, if it progresses, a gradual diminution in the visual function, which may ultimately lead to total blindness. There are two types of glaucoma:

1. Secondary glaucoma, which can appear at any time of life as a complication of some other disease of the eye.

2. Primary glaucoma, in which a rise in intraocular tension is the first chief sign. This arises most often in those over fifty years of age, but may also be found in children. As the sclerotic coat of a child's eye is still capable of stretching, the affected eye becomes enlarged, rounded and brilliant. This effect, sometimes known as having 'fine eyes,' is often known also as buphthalmia or infantile glaucoma (fig. 1). Intra-ocular tension may rise to 60 mm Hg or even higher (normal intra-ocular tension does not exceed 21 mm Hg). The cornea becomes hazy, then opaque, and vision is greatly reduced. The corneal opacity is not necessarily permanent and may disappear completely if treated at the earliest possible moment.

Glaucoma can come on early or late in life. The seriousness and rapidity of the progress of the condition depend principally on the time of its onset and the gravity of the initial symptoms. In an untreated case visual acuity can remain fairly good for a long time, if it is adequately corrected with glasses, but the field of vision gradually narrows.[11] The thinned and distended sclerotic coat may show slate-blue patches[12] which may give rise to actual ruptures of the eyeball as a result of quite a minor injury. The optic papilla at the rear of the eyeball may become hollowed out (cupped disc), with resulting atrophy of the nerve fibres in it, and the retinal vessels may become narrowed. Later, a cataract[13] may develop and the retina may become detached, in which case complete permanent blindness follows. Blinding usually results from prolonged stretching of the nerve head, which gives rise to optic atrophy. A blind eye with high intra-ocular tension may be removed to relieve severe pain. The treatment of glaucoma is designed to reduce the tension in the eye by encouraging a more efficient drainage of the aqueous humour.

In cases of congenital glaucoma, two types of malformation are found. One is the persistence of tissue of embryonic type in the irido-corneal angle,[14] and the other is an absence or malformation or malposition of the canal of Schlemm.[15]

Congenital glaucoma often appears as an hereditary disease, transmitted by a recessive type of inheritance, which accounts for the fact that in the great majority of cases those affected have normal children. A certain number of sporadic cases may be found, however, but it is not uncommon to find a close blood relationship between parents in a family affected by infantile glaucoma. This glaucoma is usually bilateral and affects boys more often than girls.

The differential diagnosis of the buphthalmic form of congenital glaucoma is from megalocornea, also a congenital abnormality, which is transmitted in a sex-linked recessive manner. This latter characteristic explains its predominantly male distribution.

In this abnormality, the cornea may have a diameter as great as 16 mm,[16] but the eye functions normally, the tension of the intra-ocular fluid is normal, and so is the tissue at the irido-corneal junction. This ocular state remains remarkably constant during growth.

The treatment of infantile congenital glaucoma is first of all medical, but such treatment is seldom sufficient in itself and surgical intervention is usually called for. In order to arrest the disease, it is essential that treatment shall be well planned, though even then it is not uncommon for the condition to recur after a long period of stability. Cases which have been neglected or treated too late usually result in blindness.

Congenital cataracts

A loss of transparency in the lens,[17] or cataract, as it is called, is not found exclusively

(10) *The coats of the eye, sclerotic, choroid, and retina, are kept in a state of elastic tension by the vitreous and aqueous humours which form the main contents of the eye. This elastic tension is called the ocular tension, which is not increased by a rise in the general blood pressure. The pressure of blood in the choroid coat is controlled by a local regulatory system which renders it largely independent of the general blood-pressure. The vitreous humour, a jelly-like substance, occupies the posterior chamber of the eye behind the lens. The aqueous humour, in the anterior chamber of the eye, is secreted and absorbed within the sclerotic coat: thus any simultaneous disfunction of either or both the two processes will have an immediate effect, in one direction or the other, on intra-ocular tension.*

(11) The visual field *is the space which the eye can see, without moving, around the point on which it is fixated.*

(12) *The colour is due to transparency of the sclerotic coat.*

(13) *Loss of transparency by the lens of the eye is called* cataract. *The papilla, or optic disc, is the point at which the optic nerve leaves the eyeball. In normal circumstances it is slightly hollowed, but in glaucoma this hollowing is greatly increased. The retina, a membrane made up of nerves and the sensory cells concerned with vision, consists of two layers, an internal one made up of the sensory cells, and an external one. When the retina becomes detached, separation takes place between these two layers and the internal layer floats off into the interior of the eye.*

in old age. It sometimes occurs in partial or even complete form in quite young children; or it may result from injury or infection of the eye, or from the disease of some other bodily system (skin, muscular or endocrine), or from diabetes. It is often not discovered until late, particularly if it is incomplete, being revealed by the child's obviously poor vision, or because it is visible to the naked eye. Such a cataract may be either hereditary or the result of some intra-uterine inflammatory process. Among hereditary cataracts there are:

1. Zonal cataract, distinguished by the opacity being in the intermediate zone of the lens, between the nucleus and the cortex, both of which remain clear. The opaque zone is of variable thickness, either homogeneous or made up of separate fine opacities and is characteristically straddled on its equator by thickenings of distinctive character, called 'riders' (fig. 9). This type of cataract rarely develops further and is almost always bilateral, but may differ in the two eyes.

2. Total cataract, which involves the whole of the lens and is nearly always complete at birth. It may consist of an opaque membrane which represents the anterior and posterior cortical layers which have become adherent, the semi-liquid nucleus having been absorbed. This is called a membranous cataract. Sometimes only the central part of the lens presents this membranous appearance, the peripheral part being of normal thickness and more or less opaque. This form is known as a 'lifebuoy' cataract (figs. 10, 11).

3. Nuclear cataract, localized in the embryonic centre of the lens and existing in three forms: *(a)* one consisting of punctuate whitish opacities which are distributed throughout the centre; *(b)* a diffuse form, in which the whole of the embryonic centre presents a greenish thickening which recalls the senile type of nuclear sclerosis; *(c)* a complete form, in which the centre as a whole appears white and firm. Vision may be disturbed to a greater or lesser extent, depending on whether both eyes are affected, but in the complete form it is poor.

There are also the following forms:

An anterior axial embryonic cataract, made up of whitish punctate opacities situated a little in front of the centre of the lens. This form does not change and leads to little difficulty in seeing.

A stellar cataract, formed by opacification of the lens sutures, which also causes little trouble in seeing.

An anterior or posterior polar cataract, localized at one pole or the other and which, although sometimes visible to the naked eye as a small white spot in the centre of the pupil, rarely affects the vision.

Congenital hereditary cataracts are usually transmitted as dominant characters, but recessive forms are often found in cases where the parents are consanguineous. In affected families, one of the possible forms may predominate, but other forms may also occur.

The embryopathies[18] which are mostly responsible for congenital cataract are German measles[19] and toxoplasmosis.[20] Such acquired cataracts can present the complete or central forms described above under *Congenital cataracts*. Cataracts following German measles can also present a form in which the lens is flattened and may become membranous. It is not accompanied by posterior synechiae, unlike a cataract due to toxoplasmosis, which is a complicated one.

Operation for congenital cataract must be performed early, ie, from the sixth month of life, if it is to be performed at all. The operation is not as simple as that for the cataract that occurs in old age, and has to be carried out in several stages. In all cases, the operation must be followed by the wearing of glasses to correct the effects caused by the absence of the lens.

Retrolental fibroplasia

When examined with the ophthalmoscope, the retina looks red because the blood in the choroid coat behind is seen through its transparent layers. If one looks towards the nasal side, one sees a pinkish-white disc with clear-cut edges; this is called the optic disc or papilla. This is the point at which the optic nerve leaves the eye, and from it emerge the central vessels of the eye, the retinal arteries and veins, which give rise to superior and inferior branches, which in turn subdivide into nasal and temporal branches. From each of these branches series of collaterals emerge. On the temporal side of the papilla one finds the macula, at which the visual acuity is maximal.[21] All these structures taken together form the fundus (fig. 2).

Retrolental fibroplasia is found in premature infants which have been kept in an incubator, perhaps for several weeks after birth. This condition, which was unknown until it became possible to rear premature infants in an incubator, was at one time found in as many as 13 per cent of premature infants that weighed less than 4½ lbs at birth. Now, thanks to special precautions taken in all units

(14) *In the normal individual the embryonic tissue at the* irido-corneal angle *is reabsorbed. Its continued presence hinders the absorption of the aqueous humour which takes place mainly at this point.*

(15) The canal of Schlemm *runs round the cornea at the irido-corneal angle and constitutes the principal escape channel for the aqueous humour from the anterior chamber.*

(16) *At birth, the cornea has a diameter of about 10 mm. In adults its diameter is about 11·7 mm, and the volume of the eye is increased by about three times.*

(17) The lens *consists of an embryonic central nucleus surrounded by an adult nucleus. The whole is enclosed in the lens capsule. The main substance of the lens consists of fibres. Those of the embryonic nucleus converge towards the anterior axial region of the lens, where they unite at a suture of Λ form, and towards the posterior region, where they form a suture of Λ form. Details of the structure of the lens can be seen with the slit-lamp microscope,*

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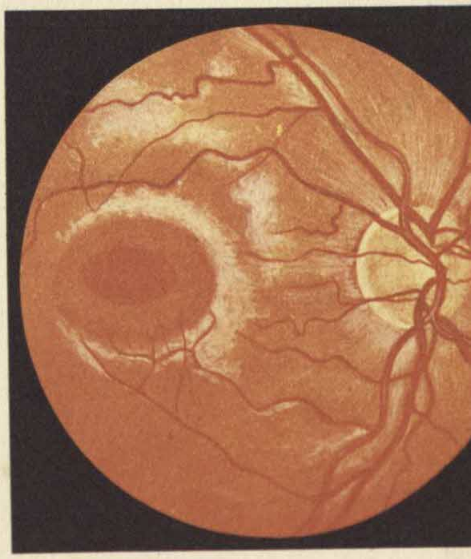


Fig. 2. The normal fundus. Right, the point of exit of the optic nerve (papilla) with the arteries and veins (darker colour) which emerge from it. Left, a reddish area surrounded by a reflection. In the centre of this zone is the macula. (Photo Dr Ménestrier).

specializing in the care of premature infants, it is becoming extremely rare. The fibroplasia arises when an excess of oxygen is given during the early management of a small premature infant. This danger is now recognized.

The fundus of the infant, whether normal or premature, is very similar to that of the adult, but differs in the pallor of the optic disc and of the periphery of the retina, and in the visibility of the pattern of the larger vessels of the choroid.[22]

Besides retinal haemorrhages, which often occur at birth but are more frequent in premature infants than in normal ones at full term, the premature infant has a tendency to show vascular retinal changes, characterized by an increase in the diameter of the retinal vessels, which become tortuous, and by the formation of skeins of new capillaries, particularly in the periphery of the retina. These may be followed by the appearance of punctate retinal haemorrhages.

Such changes may disappear completely and prove to have been no more than a source of unnecessary anxiety. If, however, they are the start of retrolental fibroplasia, these punctate haemorrhages will extend and become definite flecks and a progressive peripheral oedema, at first limited, will gradually extend over the whole retina, which takes on a dirty yellow colour. This oedema may be followed by a limited or complete retinal detachment. If it is complete, the internal layer of the detached retina may come to lie against the posterior surface of the lens and then undergo a fibrous degeneration. The space thus formed between the layers of the retina is filled by an exudate[23] which eventually becomes fibrosed. Such a sequence of events leads inevitably to total blindness. Happily, this does not occur in most cases, and sometimes the retina may become reattached. Between these two extremes there are various possible states.

The severe form accounts for some 30 per cent of fibroplasias. The more benign form, not leading to disturbances of vision, makes up some 60 per cent. In the remaining 10 per cent there are some persistent sequelae to the condition. In premature infants, fibroplasia usually begins some four to six weeks after birth, often coinciding with what would have been the normal date of birth. Its development may take from four to twelve weeks. There is no medical or surgical treatment for this condition, and the best method of prevention is to ensure that the care of premature infants is in the hands of specialists.

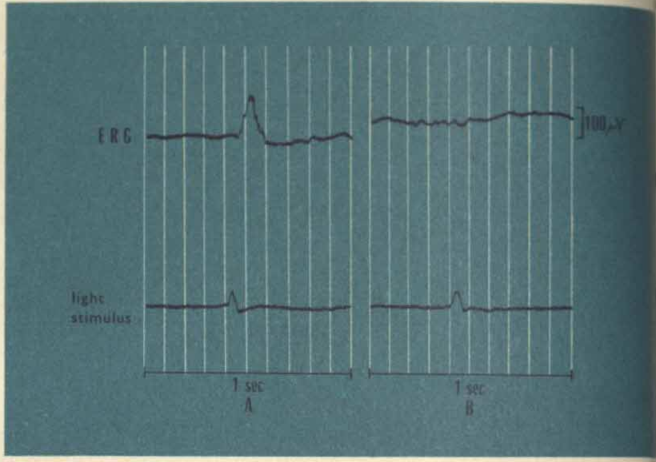


Fig. 3. An electroretinogram. A shows normal response to a light stimulus. B, taken from a case of Leber's congenital tapetoretinal degeneration, shows no response to the light stimulus.

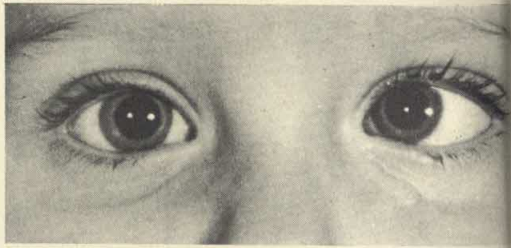
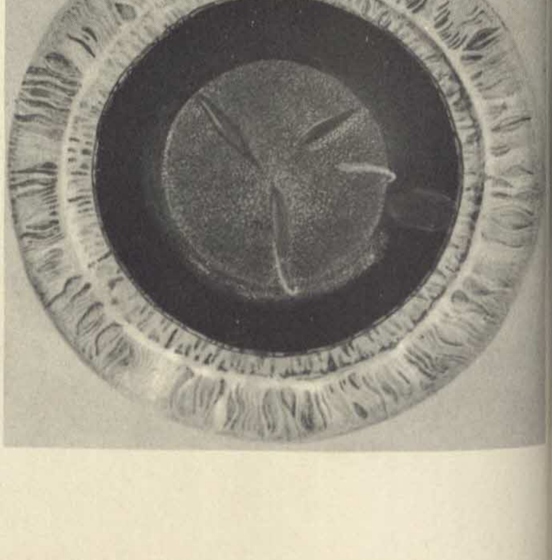


Fig. 6. A convergent squint. The left eye is deflected inwards. (Photo Dr Ménestrier).

Fig. 9. Typical zonular cataract. It occupies the cen of the lens. At the edge of the discoid opacity are t riders, shaped like wedges. (Photo Dr Ménestrier).



which allows examination to be made during life of the anterior structures of the eye and the vitreous humour, if the lens is transparent. Under normal circumstances, the iris rests on the lens without adhering to it. If the iris becomes inflamed it may adhere to the anterior surface of the lens capsule, forming anterior synechiae, which show the presence of some inflammatory or traumatic process in the eye.

(18) *An* embryopathy *is an illness which affects the child during its intra-uterine life.*

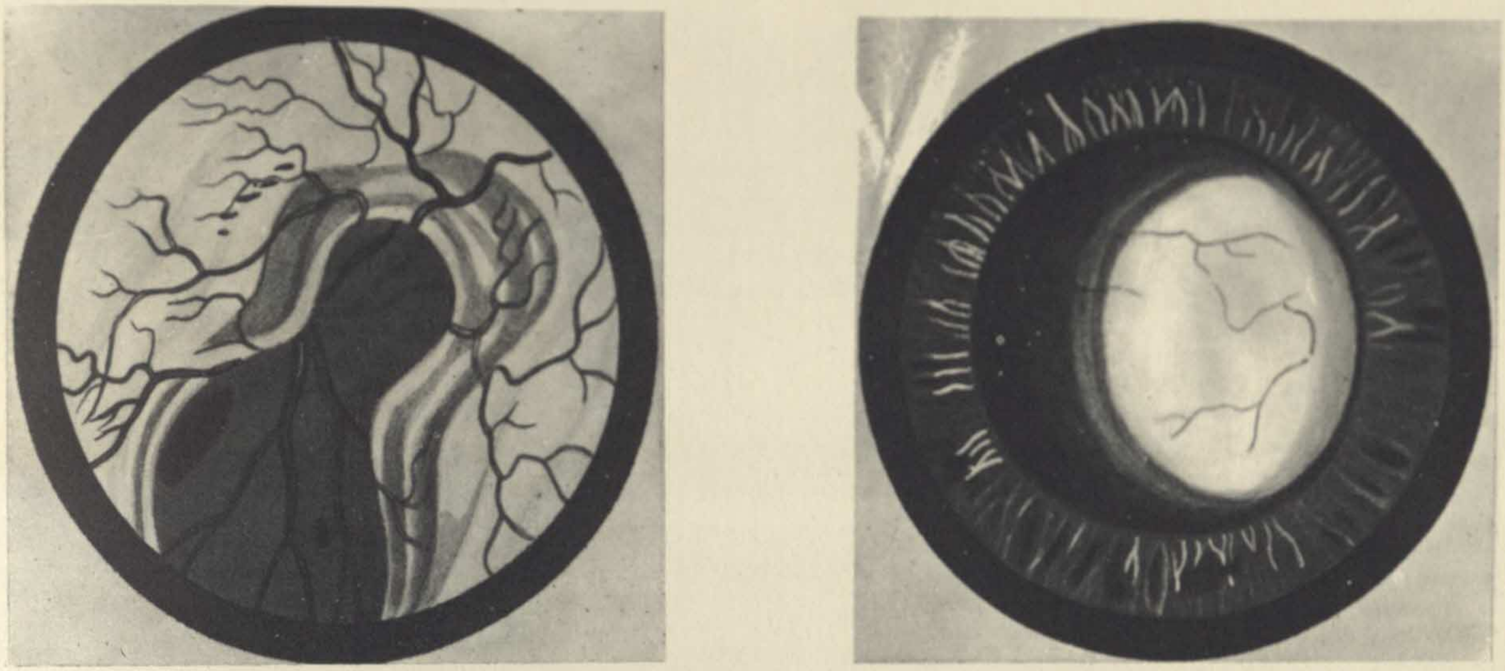
(19) German measles *is a disease associated with a rash which is, in general, like that of measles proper. If a pregnant woman contracts this disease during the first three months of her pregnancy, it may lead to the appearance of various malformations: cataract, congenital deafness and dumbness and cardiac malformations.*

(20) Toxoplasmosis *is a generalized infection, either congenital or acquired, caused by protozoa. In the congenital form, the ocular and cerebral manifestations predominate.*

(21) *The absence of sensory cells in the papillary region gives rise to the 'blind spot' which was discovered by Mariotte. It is not normally noticed either in binocular vision, as the two blind spots do not coincide, or if only one eye is used, because the eye continually makes small movements.*

(22) The choroid coat, *a vascular coat, has two layers. The inner one, next to the retina, is made up of fine thin-walled vessels which, being transparent, give the fundus its red appearance; the outer one is fixed to the sclerotic coat and is made up of a network of larger vessels.*

(23) *An* exudate *is an aqueous liquid containing mainly white blood cells and fibrin, which filters through the walls of the blood vessels into the neighbouring tissues where inflammation is present. If the exudate is not reabsorbed, the fibrin gives rise to fibrous tissue.*



Figs. 4 and 5. Retrolental fibroplasia. Left, an annular peripheral retinal detachment. The illumined retina forms folds which bulge towards the lens (stage 5). Right, a whitish fibrous membrane stuck to the back of the lens (stage 6). (After Lelong et al. Présse Médicale, 59, *705, 1951).*

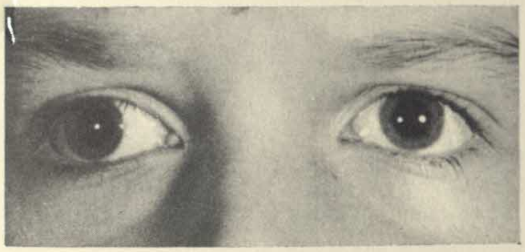


Fig. 7. A divergent squint. The right eye is deflected outwards. (Photo Dr Ménestrier).

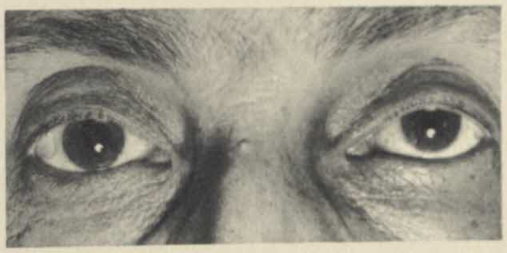


Fig. 8. A vertical squint. The left eye is deflected upwards. (Photo Dr Ménestrier).

Fig. 12. Stellate cataract, seen from the front

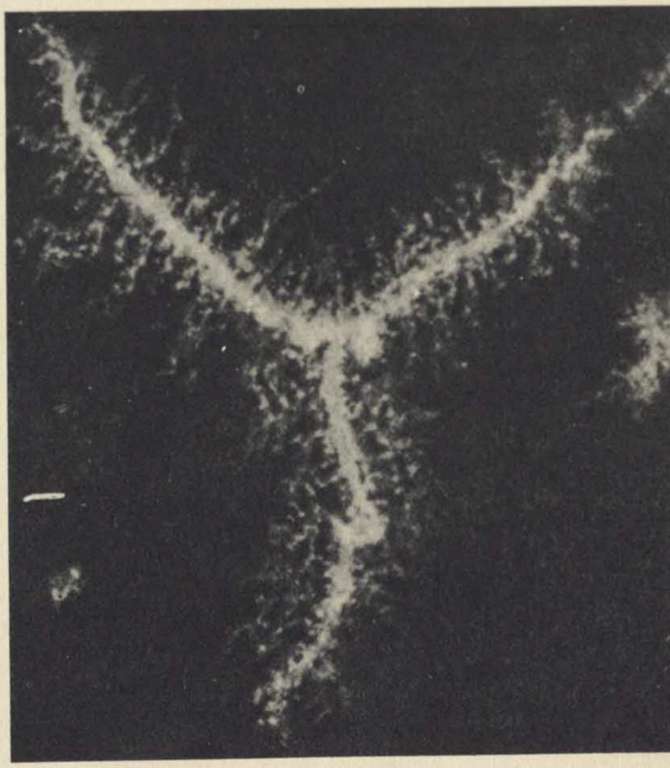


Fig. 10. Lifebuoy cataract, seen from the front. Only the central part of the lens has a membranous appearance. (Photo Dr Ménestrier).

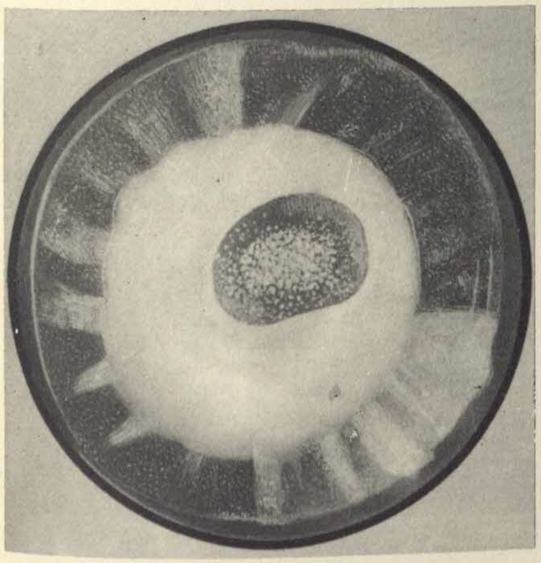
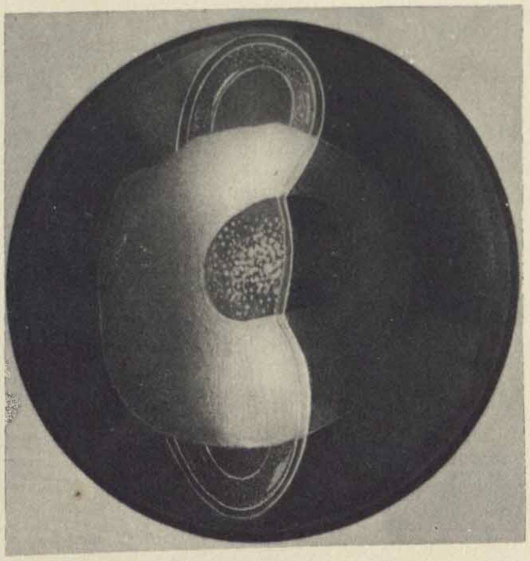


Fig. 11. Lifebuoy cataract; an optical section seen by the slit-lamp microscope, showing the sinking in of the centre. (Photo Dr Ménestrier).



Mongolism

Raymond TURPIN

Mongolism is a relatively rare disease which may appear at birth in families with no previous history of abnormalities. Mongoloid children are backward and develop up to the age of twenty at the most. Nearly all of them die of pulmonary tuberculosis. The origin of mongolism was unknown until Professor Raymond Turpin and Jérome Lejeune showed it to be associated with a chromosome abnormality analogous with that previously noted in certain animal and plant species; namely, the appearance of a very small supernumary chromosome. However, the causative agent which leads to this abnormality is still unknown.

Mongolism, a congenital disease[1] which profoundly disturbs growth and reduces the expectation of life, offers a remarkable example of the possibilities opened up by the persevering and well-directed study of a pathological curiosity.[2] The discovery, after thirty years of study, with my pupils Jérome Lejeune and Marthe Gautier, of the supernumary chromosome[3] that characterizes the hereditary basis of mongolism has given us the key to the condition under which this disease appears and has opened a previously unknown chapter in human diseases caused by chromosomal abnormalities.

As a result of this discovery, the mental and physical characteristics of mongols have once more become the object of study. Their mental state is characterized by a backwardness of greater or lesser degree and by emotional disturbances. The intelligence quotient averages between 35 and 50 and varies in respect to this mean value between the limits of plus or minus 0·5 per cent. Emotional disorders are not found in mongols at the lower end of the scale. They appear more and more as the intelligence quotient increases, and may give rise to anxiety states.

The physical condition is characterized by a complex of constitutional disturbances. A fully-grown mongol is noticeable because of his small stature, corpulence, rounded head, and his face, which gives the impression of a human face that embryonic development has not quite succeeded in perfecting. The fine hair, the low forehead, the oblique eyelids, the short depressed nose, small mouth, and small badly-formed ears all contribute to a characteristic appearance. The abnormal general development, affecting the skeleton as well as the soft tissues, leads to the appearance of a whole series of further abnormalities that we cannot even begin to list here. Some of these have a diagnostic value, especially the abnormalities of the hands. These are thick and short, and the structure of the skin of the palms varies considerably from the normal. Their classification is used to calculate an index which is sufficiently characteristic to allow us to make the diagnosis of mongolism with no more than a five per cent chance of error (see illustrations on pp. 136–7).

Another sign of the disease is to be found by examination of the white corpuscles of the blood. The nuclei of the polymorphonuclear leucocytes are less lobulated than in normal persons, and from this we can calculate an 'index of nuclear segmentation' which gives a figure below the normal mean.

Other abnormalities lead to disturbances of function in the nasopharynx (adenoids) and in the function of the eyes. Mongols often suffer from hypermetropia, squints, nystagmus[4] and occasionally cataract. The free edge of the eyelids is often the site of chronic inflammation (blepharitis).

Mongolism is often complicated by numerous malformations. These may be parietal (hernias), digestive (malpositioning and stenoses), genital (disturbances of development), urinary and especially malformations affecting the heart and aorta. These latter are the most important because of their frequency and gravity. On them depends to a great extent the mongol's expectation of life, especially since the advent of chemotherapy and antibiotics.

(1) Congenital. *A condition already present in an individual at birth.*

(2) *At the beginning of the last century, Esquirol had already suggested the existence of this type of idiocy. He noted the small rounded head and the oblique eyelids. A few years later, Seguin also noted these particular aspects, as well as the thick, fissured tongue, and, struck no doubt by the ease with which the skin was damaged, called the condition* 'idiotie furfuracée' *or 'branny idiocy'. Soon afterwards, Langdon-Brown, trying to support his attempt at an ethnological classification of idiocy, defended the analogy between the features of these patients and those of the Mongolian race. As a result, the term 'mongolism' became generalized, although its theoretical basis of morphological evolution can no longer be sustained. For many years, the disease was reputed to be a rare one and was scarcely spoken of. Bourneville, who separated it clearly from myxoedema, is said to have found only a score of cases throughout his career. Following this period of lack of interest, there has been a one of uninterrupted study extending over the past forty years. These studies have revealed the curious conditions of its appearance and the very numerous mental and organic peculiarities of the disease. The attention, first of doctors and then of the general public, was awakened, as the social importance of the condition and also the difficulties of treatment in or out of hospital, become clearer.*

The new-born mongol is already profoundly affected by the disease. Even if he is born at full term, his physical weakness is severe; he looks like a stuffed doll, with his little round head, and has great difficulty in adapting himself to normal breathing and feeding. He is also very susceptible to all types of infections. But his expectation of life depends, particularly today, on the extent of his various internal malformations. He is characterized by a marked muscular weakness and is retarded in his ability to hold up his head, to sit up, and to walk. The development of the teeth is disorderly rather than retarded.

The weakness of the nervous system and of the mental functions is just as marked. Old reflexes persist, the child is late in smiling and in showing signs of intellectual awakening. The first signs of talking and appreciating the significance of language do not appear, or are so inadequate that even the most optimistic parent becomes anxious. From then on, the mental and physical characteristics develop more obviously. At the time of puberty, the abnormalities of behaviour are often especially marked, but once this stage is passed, the mongol is usually quiet, affectionate, easily satisfied, and above all, lazy, showing little inclination to use those abilities of reading, writing, etc, which with great difficulty have been instilled into him. The reproductive functions, to judge by some rare observations of pregnancies that have proceeded to full term, and by examination of male sperm, reach the adult stage with no particular delay.

As time progresses, the mongol, already short in stature, begins to put on weight and seems to be threatened by premature ageing, the results of a slowing down of the functions of the thyroid gland. Mongols are also characterized by their predisposition to various diseases. Although they are seldom subject to allergic diseases (eg, asthma) and are rarely epileptic, they are very prone to tuberculous infection, which, with leukaemia, are two of the commonest causes of death.

The explanation of the conditions under which mongolism appears and of certain of its peculiarities must be sought in the chromosomal abnormality which is characteristic of the condition. The supernumary chromosome which has been discovered in the chromosomal make-up is very small. It appears, at the prophase, in the form of a V with a terminal centromere,[5] prolonged by a small heterochromatic arm with a satellite.[6] Called Vh by the French experts, in the international nomenclature it is No. 21. The normal non-sexual body-cells should contain two chromosomes-21, but those of the mongol contain three; they are 'triplo-21'. Mongolism is thus a case of trisomic chromosomes, showing that even the human race can exhibit this type of abnormality, which has been known for a long time in certain species of animals and plants.

If one wished to give an experimental example equivalent to that of the mongol, the *Drosophila* (fruit-fly) triplo-IV would be a good one. This comparison leads us to think that triploidy may be due to non-disjunction at meiosis, with the formation of abnormal diplo-21 gametes.

This theory of the abnormality has the following great advantages: it takes into account the frequency of mongolism—one in every 600 to 700 births, which is close to the figure for non-disjunction found experimentally; it accounts also for the greater frequency of the condition in the offspring of older mothers, which parallels the greater frequency in experiments of non-disjunction following X-ray irradiation in aged ovaries; it agrees with the occurrence of mongolism in both members of a pair of identical (uni-ovular) twins, whereas it rarely occurs in both of non-identical twins; and it also accounts for the offspring of the union between a mongol and a non-mongol being either normal or mongoloid.

However, the condition of mongolism may be complicated by other abnormalities. There may be a supernumary Y chromosome, giving rise to Klinefelter's syndrome.[7] Or there may be fusion at the ends between two acrocentric chromosomes (translocation).[8] We found the first example of the latter in a child with vertebral malformation. Occasionally, a translocation may complicate the mongoloid trisomia, in particular the translocation 21 ~ (13, 14 or 15). This translocation has been found in the non-mongoloid mother of one or two mongol infants. It may lead to the exceptional occurrence of the condition in several children.

Certain peculiarities of mongolism can be explained on the basis of 'genetic over-dosage' for which the supernumary chromosome 21 is responsible, ie, the analogy between the structure of the palmar skin in mongols and that of lower primates. This example of 'phyloteny'[9] can be given a genetic explanation. Similarly, disorders of tryptophane metabolism can be interpreted as the result of genetic over-dosage.[10]

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(3) Chromosomes: *see the chapter on Heredity, p. 138 of this volume.*

(4) Nystagmus. *Short irregular oscillatory movements of the eye which are rapid and constant.*

(5) Centromere. *Each chromosome bears a small body known as the centromere, situated at the narrowest point. In the course of the process of cell division a spindle appears, each pole of which corresponds to one of the daughter cells. Each chromosome divides into two chromatids. Each chromatid attaches itself to one of the fibres of the spindle by means of its centromere. It is thus guided towards the daughter cell for which it is destined, where it forms a chromosome again.*

(6) Satellite. *A sort of hollow expansion carried on a small arm at the end of certain chromosomes.*

(7) Klinefelter's syndrome. *An abnormality in the embryonic development of the testicles which leads to sterility and a diminution in virility.*

(8) Acrocentric chromosome. *A chromosome which has its centromere very close to one end. Two acrocentric chromosomes, one of which has lost its centromere, can fuse. This centric fusion forms one variety of chromosomal recombination.*

(9) Phyloteny. *Return to an earlier stage of evolution. It comes from the Greek* phule, *a tribe (a source from which a series of beings originates) and* teino, *'I retain'.*

(10) Genetic over-dosage. *A supernumary chromosome in fact brings to the cell a superfluity of genes, the hereditary factors which are carried on it.*

Fatigue and anxiety

Charles BRISSET

Where normal and pathological conditions begin to overlap, that is to say, where general medicine touches on psychological medicine, there are a number of facts sufficiently well-known to the man in the street for it to be possible to refer to them without ambiguity, yet at the same time they are still something of an enigma to specialists. These include the concepts of fatigue, pain, and anxiety, which are experiences common to all of us, but which the specialists cannot define without distortion. They must either be accepted in the sense in which they are used by the man in the street, or they must be chopped up into fragments which at best can be explained only partially in terms of the concepts and scientific knowledge which we possess. But though this may make it possible to see certain details more clearly, it makes it impossible to grasp the whole of the sensation, however familiar it may be. This is the crux of modern discussion about the methods used by the social sciences, especially in medicine, on the limits of the experimental method, or psychosomatic problems.

Fatigue and pain

Let us take a simple example and tackle it by the methods used in physiology. Muscle fatigue results after a certain period of muscular effort. The contraction of the muscle and the local changes which eventually result from it are within the sphere of experimental knowledge; they may be called 'objective'. The intimate details of muscular contraction are very complicated. They include not only rearrangements of the structure of the myofibrils,[1] but also changes not yet completely understood in the cellular proteins. Nevertheless, they can be investigated by laboratory methods and techniques.

The same applies to the relations between muscular contraction and the body's metabolism. The mechanism of muscle contraction occurs in isolation only when we are studying it in the laboratory; otherwise it fits in with the general activity of the body. It depends on the reserve of glycogen, on the state of the endocrine organs (thyroid, adrenal), and on the functioning of the heart, the lungs, and the kidneys. Here the central nervous system is involved, both as the originator of the contractions and as the co-ordinator of these various functions. In other words, the physical, chemical and physiological aspects of muscular contraction and fatigue lend themselves to observation by objective methods; that is to say, they can be precisely defined and divided into their various parts. In difficult cases, the experiments can be repeated and verified by others. The central nervous system also operates in another sphere: it places the organism in contact with its environment. Here, new aspects of muscle contraction and fatigue appear, but these are not capable of reduction to well-defined physiological patterns. The ordinary man is well aware that his feelings of tiredness vary according to circumstances and that proper training enables him to do more without feeling exhausted. A powerful stimulus may push him to activities that would have been beyond him at any other time; conversely, a negative stimulus (boredom, conflicting interests, fear, and so on) will lead to fatigue appearing much earlier than it would otherwise have done. Psychologists are trying to understand the motives behind these facts by using objective methods.

Such studies enable us to get to grips with the problem of muscle fatigue and the intervention of factors which are referred to variously as personal factors, psychological factors, social factors, or merely 'significant' factors. But these factors are not easily studied objectively by a third person. They require other modes of thought, other methods of study, modes and methods which can only be explained in the first person. 'I am tired' is a clear statement, no matter by whom it is made. On the plane of ordinary communication it is also clear to whoever hears it. But it cannot be 'explained' in the sense ordinarily used in the natural sciences; on the plane, that is, of experimental or objective observations which try to reduce the factors to some common denominator.

In order to take this phenomenon into account, we must pass from the plane of spatial data to that of chronological data. It is the history of the person involved, a history perpetually in progress, and which includes not only his past, but his whole world, his plans, his system of values (moral, aesthetic, and

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(1) Myofibrils *are the elements which make up the muscles.*

(2) *The biochemist's ideas on the real cause of the Marathon runner's death are very different from those of the psychologist (see the chapter on A Chain of Chemical Reactions by W. W. Nowinski, p. 40, Volume 1 of* The Living Universe). *Nevertheless these two points of view are not in fact contradictory; the theory that the runner died as the result of acidosis does not exclude the possibility that his excessive fatigue was unnoticed because of the psychological reasons mentioned.*

mystical), his beliefs, his 'complexes' and his unconscious, which alone will enable us to understand why he gets tired at a certain moment, or why fatigue disappears when he is motivated, and may continue to pass unnoticed beyond a dangerous point when he is activated by a very strong motivation. It will show us why fatigue appears very early under the influence of certain negative motives.

Whatever is applicable to the simplest example, that of acute muscular fatigue following prolonged or intense effort, is naturally applicable to other types of fatigue. Specialists in fatigue tend to classify fatigue by 'situations'. The fatigue of the sportsman, industrial fatigue, fatigue in the business man, in the soldier, the airman, the exile, the worker in the tropics, etc. This 'normal' type of fatigue contrasts with pathological types of fatigue, such as those resulting from disease of the thyroid and adrenal glands, etc. Fatigue can also be classified according to the system involved, muscle fatigue, sensory fatigue, etc. All these categories, necessitated by the demands of scientific investigation, show how difficult it is to pin down this phenomenon of fatigue.

One example which is not very well known, but which clearly demonstrates the influence of the *personal* element in all types of fatigue, is that of auditory fatigue in workers whose occupations subject them to very loud noises for long periods. Thomatis showed that a large number of technicians employed in testing aero-engines were liable after six months or so to become deaf as a result of the noise. He also measured the volume of sound to which musicians in a symphony orchestra were subjected, and found that it was equal to and sometimes even louder than the noise in the aero-engine workshop. Now, one does not find any occupational deafness in musicians. Thus it would appear that noises *which make sense* are less harmful than those which do not. One can see from such an example the importance of 'form' and its intimate connection with the variables in the personality of the subject.

Everything which has been said about fatigue is true also of pain. The psycho-social factors make it impossible to compare pain as between one person and another. The thought of an amputation without anaesthetic makes one shudder. It is probable that today no one could withstand such pain and that it would prove fatal. But Baron Larrey, after the battle of Eylau in 1807, amputated forty legs through the thigh with no other anaesthetic than a glass of rum from the *cantinier*. Yet the wounded did not die of the pain. It was the inescapable necessity of putting up with it that made it possible for Napoleon's soldiers to do so. And it is the fact that we now know it would be unnecessary to do so that would make it seem quite insufferable and might well prove fatal.

The subjective aspect of fatigue

These reflections allow us, if not to understand, at least to envisage the background against which we can begin to study these 'psychopathological' types of fatigue which bring people to the psychiatrist and are sometimes distinguished from other types by the term 'asthenias'. This background is made up of facts, of which the history of the patient, the subjective side of the problem, and its unconscious significance are the most essential. The actual local changes can only be envisaged as occurring in the nerve centres in the form of predisposing factors. It is not surprising that the depressive, worn down by his feeling of complete unworthiness, or the neurotic, shuttled back and forth between various contradictory motives, become fatigued to a greater extent, and certainly more permanently, than a sportsman or a worker. The loss of any apparently valid reason for making the slightest effort renders such an effort completely impossible—even more completely than would muscular exhaustion. In severe cases of melancholia, the patient, who is convinced of the harmfulness of the smallest action, remains immobile and speechless, in a stupor. In such a case, the fatigue is entirely the result of the way the patient looks at things, or the way he lives in his own little world.

We may stop here to glance at the historical episode of the original Marathon runner who died after delivering his message. This was an example of the type of situation in which an extremely strong motive may lead to the suppression of the feeling of fatigue, or at least of the dangerous degree of fatigue which has been reached.[2] Such examples, the complete exhaustion of the athlete, for instance, may be relatively rare in the field of acute fatigue, but they are not at all rare in cases of chronic fatigue. Some people wear themselves out more or less quickly because they cannot (or, at least, think they cannot) moderate their efforts. Examples of this are found among overworked mothers of large families, among business men who undertake more than they can reasonably cope with, and among young workers who are trying to carry

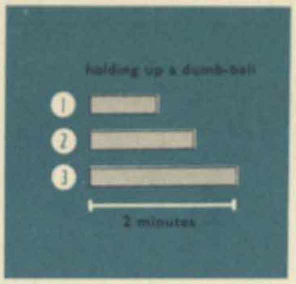


Fig. 1. Records of the time for which a dumb-bell can be held up. (1) After a simple request. (2) After hypnosis and suggestion. (3) After the subject has been asked to do even better, with a reward of five dollars if successful. (After Robert S. Schwab, Motivations in Measurement of Fatigue in Symposium on Fatigue, *by W. F. Floyd and A. T. Welford, H. K. Lewis and Co., London, 1953).*

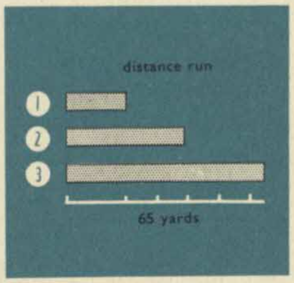
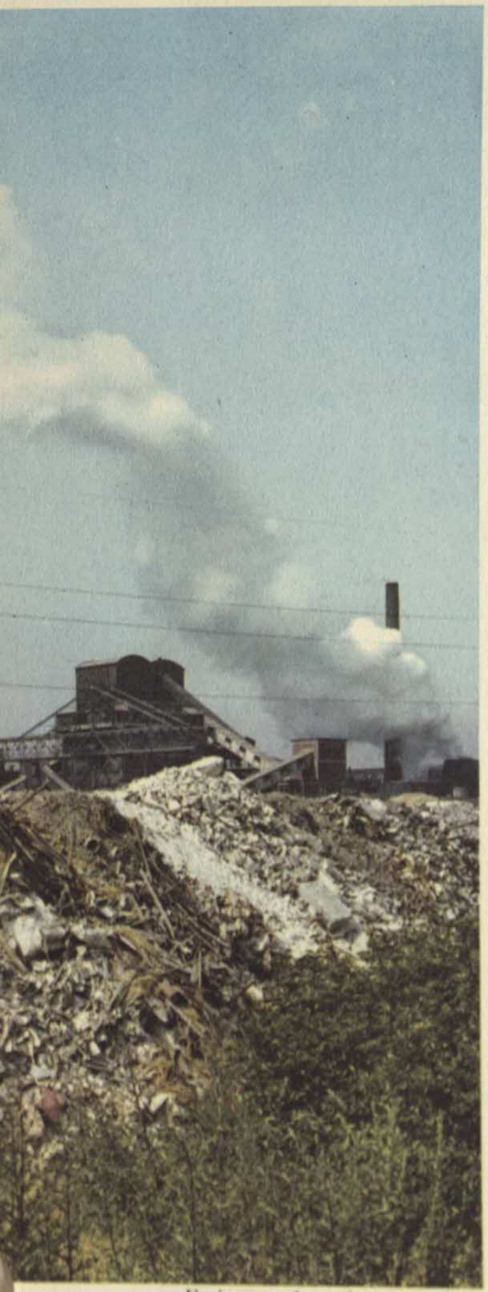


Fig. 2. A ticket-holder who arrives late for his train will not run more than twenty yards if there are still two trains which he can catch. He will run sixty-five yards, shouting and waving his arms, if it is the last train of the day. (After Robert S. Schwab, loc. cit.*)*



Fatigue and anxiety are phenomena which must not be considered as organic lesions, but rather as a total upset of all the physiological and psychological functions of the individual. The environment in which he works and lives (see the photo above) is equally responsible, in the same way as the emotional or social experiences, whether conscious or subconscious, which have affected him. The doctor tries to take note of all this, so that he can help the patient. (Photos Lod).

through some difficult job. Others misuse some organ or system of organs (always the same one) by constantly overloading it. One speaks of the overworked heart of certain athletes, but one might equally well speak of the overworked digestive apparatus of the glutton, or the overworked nervous system of business men in high positions. In all these cases it will be seen that the fatigue is not noticed, or at all events not noticed soon enough.

This illustrates one essential aspect of fatigue; that is, of sounding the alarm in the body and producing changes in behaviour to counteract it. (Pain has the same function, of course.) Thus fatigue has its own functional role, a normal one. We need to feel fatigue to avoid becoming ill.

Fatigue must be considered from two aspects. The first relates to quantitative considerations and can be related to objective spatio-temporal co-ordinates. It is the *resultant-fatigue* of the total functioning of an organism. For any given organism this fatigue is proportional to the effort involved and it ceases with rest. The other aspect is subjective and depends on personal factors involved in its appreciation; it can be called *estimation-fatigue.* Obviously, it can vary greatly, since it may appear even before work starts, or, on the other hand, may not appear until fatigue has become a really serious matter. Such fatigue is not proportional to the effort involved, nor is it relieved by rest. In all cases of fatigue both these aspects are present in varying degree.

Anxiety, a complex phenomenon

The phenomenon of anxiety is illuminated by our study of the related theme of fatigue. There is in fact a close parallel between the two states. Anxiety, however, is naturally much more closely related to our subjective experiences; so much so, in fact, that some people are unable to see what unites it to the function of the organism; that is to say, how it fits into our psycho-biological unity. It is an experience known only to man, a peculiar variant of pain; in fact, a type of estimation-pain paralleling estimation-fatigue. It would seem that though an animal can experience fear, and its extreme case, panic, only man is capable of understanding the progress of his life in such a way that he can gather from it an estimation of the risks he is running. This leads, if he is correct, to normal anxiety, or if he is incorrect, to pathological anxiety.

This simple idea is sufficient to dispose of the supposition that anxiety results purely and simply from the stimulation of such-and-such a nervous centre. Something which depends to so large an extent on subjective sensations and their variations cannot be reduced to a simple nervous phenomenon. But if we refuse to believe in such a simplified explanation, this is not to say that we do not accept certain local co-ordinations. It is merely that we refuse to believe the mechanical explanation, or that it is possible to provide a *total* explanation in terms of physico-biochemical co-ordination. This said, we must equally oppose those who would define anxiety as a 'purely psychological' phenomenon and refuse to accept that biochemistry is also involved. This problem, like that of fatigue, must be studied in relation to these two aspects; that is, in relation to the psychosomatic reality of anxiety.

The fact is that 'anxiety centres' do not exist, in the sense implied by a purely mechanistic interpretation, but there are certain spatial co-ordinates of anxiety, certain cerebral circuits which by their arrangements lead to sensations of anxiety. According to modern neurophysiology, there are large areas at the base of the brain, including the brain stem, the inner part of the temporal lobes, and perhaps also the thalamus, which are concerned with these effects. Direct excitation of these centres can occur in certain cerebral diseases; for example, what is called 'temporal lobe epilepsy' can show itself through anxiety. It is probably in these regions that one finds the effects of such therapeutic measures as electric-shock treatment and those of various drugs. There are also nerve receptor-organs which have particular connections with these regions and which, when stimulated, cause feelings of anxiety. These receptors are found in various organs innervated by the autonomic nervous system, which is concerned with visceral sensitivity. As a result, certain well-known types of anxiety are set off by peripheral stimulation. The best known is probably anginal pain from the heart, and there are others. Diseases of the viscera are often accompanied by a degree of anxiety owing to this particular connection.

But anxiety in actuality, in the feeling of the patient, is quite another thing from a painful stimulus. What gives it its own particular characteristic, its personal aspect (never quite the same from one patient to another) is the fact that it is intimately associated with the whole life-history of the sufferer. It might be said that at one extreme visceral pain occurring in a well-integrated person at a favourable time may be little more than a painful stimulus;

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in fact, hardly an anxiety at all. At the other, a comparable pain occurring in a weak person already affected by anxiety may be a real catastrophe which disorganizes his whole outlook and leads him to experience that acute fear of death which is sometimes described by persons in this state. Such examples are well known to all doctors. Certain sufferers from cardiac angina, once they have passed through the first crisis, recognize their pain and are no longer scared by it. Others become, or perhaps are already, neurotic, and live in fear of death.

Thus we see that for the anxious, the outlook on life is entirely bound up with the whole theme of anxiety.[3] It is at one with their characters, re-lived at each instant and renewed by the most trivial incidents. A well-integrated person, on the other hand, is able to detach himself, at least partially, from painful experiences and so to reduce by so much the burden of his anxiety.

Pure anxiety and its problems

The most interesting problem of all is that of pure anxiety, apparently without physical foundation, yet it comes on often without any organic disease being detectable. The work of Freud has enabled us to understand that this type of anxiety is also a psychosomatic manifestation.

Psychoanalytic procedures have shown that anxiety is a substitution response. It results from a need of the organism which cannot find any relief in an adaptive response. Let us say, to simplify the issue, that it results from the actual impossibility (often due to imaginary factors) of discharging some sexual or aggressive tension. Its content, which gives it its particular character of an unrealized conflict, is thus some wish, originating in a fundamental ambiguity, which cannot be recognized and which is repressed by both conscious and subconscious social pressures; a stretching out towards the accomplishment of the desire and yet held back from it by an imaginary sense of guilt.

A wish that is stimulated but not recognized: this is the psychoanalytical formula for anxiety. A wish that is recognized can lead to several solutions; it may be carried out, or a postponement of the carrying out may be accepted; or a change of the conscious object may be substituted (sublimation); a latent, unrecognized wish acts as a nebulous psychosomatic generator of malaise and anxiety.

When Freud first discovered this formula for anxiety, he applied it to the expression of sexual feelings. Then he realized that it applied also to old emotions which had not yet been properly overcome. Finally, he applied it also to aggressiveness, since a wish can be either positive or negative. Let us take two examples.

Homosexuality is a type of sexual experience which is alive in all of us and is always liable to show itself. Society as a whole strongly condemns this tendency. Thus many people are incapable of recognizing it and believe themselves completely devoid of it. But it can happen that the circumstances of life reveal to such a person the presence of his latent homosexuality. Some are then affected by acute anxiety amounting to panic, which is well recognized by psychiatrists. This tremendous anxiety is due to the refusal of the person to recognize the presence of the tendency which he repudiates. The ordinary defences of the organism are no longer sufficient to suppress it and anxiety is produced as a final desperate defence which, if allowed to persist to the bitter end, will wreck the whole personality rather than allow the repressed wish to be recognized.

'Repressed anger' is the exact equivalent in the field of aggressiveness of what has just been described in terms of the libido. The person who, once again, for social reasons, has suppressed and relegated to the unconscious mind such passions as these is therefore unable to recognize consciously the hate which his mother or father inspires under certain circumstances, and he feels only the anxiety provoked by the internal struggle. In such cases of what is called 'psychogenic' anxiety it is important to realize that the physical manifestations are exactly the same as those found in cases of anxiety aroused by outside influences, which we spoke of earlier. One finds the same changes in blood pressure, in capillary reactions, in the blood vessels, in the pulse, etc. The effect is basically the same, whether it is brought about by external or by central influences; it is an acute psychosomatic disorganization.

The extreme specialization of medicine to which we owe most of the advances of the past hundred and fifty years makes it difficult to restore the essential unity of the patient as a subject. It is becoming more and more evident that diagnosis and treatment are nevertheless impossible without such an approach. The 'medicine of the subject' must complement the 'medicine of the object'. This is the central belief of what we call 'psychosomatic medicine'.

(3) *Under the theme of anxiety the psychologist understands all the morbid imaginings which may give rise to anxiety. These include metaphysical views and those on personal destiny, whether concerned with self-estimation or the estimation of others, health, social position, etc.*

Experimental psychology

Michel GOUSTARD

Psychology is one of the social sciences which deal with man's relational life, that is, with the contacts between him and his environment. In its experimental aspect, psychology studies the many mechanisms, functions, and operations concerned with the various types of adaptation of the human being to his external environment, of which he is both servant and master. Psychology, therefore, maintains natural links with the scientific disciplines which in their various ways analyze and describe different aspects of adaptation. These include biology, physiology, neurology, sociology, and, from the aspect of abnormality, general pathology, neuropsychiatry, and psychopathology.

It is one of the modern sciences that are developing with great vigour and is being applied in all sorts of spheres, from agriculture to publicity, from fishing to space travel, from the arts to industrial psychology, etc. Here we shall be dealing with two important aspects that affect the whole of its development.

1. Psychology has a tendency to draw into its research orbit biology, neurophysiology and sociology; that is, all aspects of man. Because of this, pathology must also be involved. A synthesis develops between observations made at three different levels. The first concerns the higher level of integrated *behaviour*. It shows that all behaviour has some sense or meaning and therefore cannot be simply related to some physical phenomenon. The second level comprises *neurophysiology*, *neurobiology* and *endocrinology*. This emphasizes the importance of the subcortical regulatory centres and the connections between cortex and subcortex and between the cortex and the organs, with an influence that extends to the chemo-physical mechanisms of intracellular equilibrium; it also emphasizes the pre-eminent role of the nervous system with regard to local and specific factors both in disease and treatment. The third level is that of *psychosomatic* medicine, with emphasis on non-specific disturbances and the importance of the background in the aetiology of non-specific organic disease. In short, it can be said that psychology is joining biology and physiology as the third of the fundamental sciences of medicine (Boss, 1960).

Psychology, or more precisely, psycho-biology, can be considered a major influence in the present-day development of the sciences of man, both theoretical and applied. There must be no mistake about the meaning of 'psycho-biology': it implicitly excludes the concept of a mind–body dualism. The living organism is not made up of a biology to which a psychology is added as a sort of extra: it is a whole which by its very nature possesses two poles, one biological, the other psychological, each essentially complementary to the other. This is not just a loose connection, but a true interrelationship in which the one helps in the comprehension of the other and the two interact co-operatively. It follows that any disease, whether it be primarily organic or psychological, will affect the whole organism and its responses. In considering treatment, this fact must be borne in mind.

2. The second aspect is the introduction of the fourth dimension, time, into human sciences. This is of considerable importance, for it alters our view of man. The human organism and its mental life are not formed in a vacuum, but in relation to their environment, to the persons with whom they are brought into contact, and to the course of time. This means that the circumstances of the environment and of development through time are a feature of the development of the body, the intelligence, and the emotions. Any illness, even though it predominantly affects one of the poles, mental or physical, cannot be considered in terms of this effect alone, nor can it be properly treated unless one takes into account the integrations in space and time which make up the patient's history.

The perspective offered by the bio-psychological evolution of species shows that it constitutes a temporal integration on a large scale. It is not only *ontogenetic* but *phylogenetic*. In biology, physiology, and psychology man appears in relation to the rest of the animal world. He finds himself in a total situation which shapes him and helps to explain him, and at the same time he shows his own specificity. The problem of specifically human structures is not entirely speculative; it directly concerns pathology. A too narrow point of view reduces the physiology or psychology of man to the same level as the physiology and psychology of animals. From

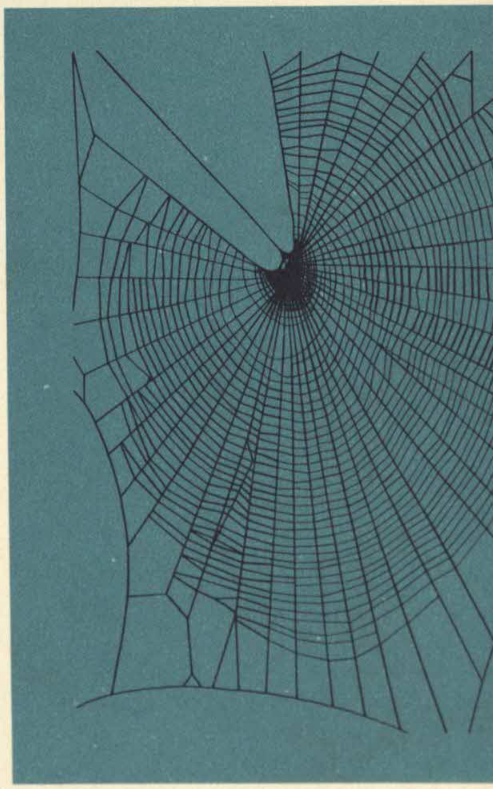

Fig. 1. The web of the spider, Zillax notata, *as spun under natural conditions. Note the scarcely perceptible irregularities.*

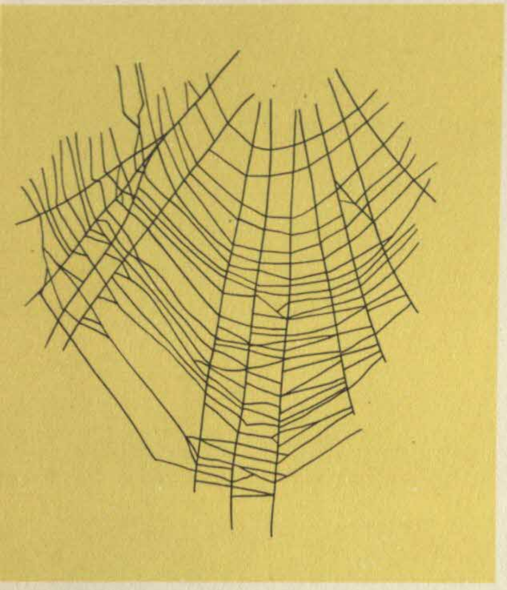

Fig. 2. Web of Zillax notata *spun under the influence of the excitant drug, pervitin. The very irregular web demonstrates some psychological disturbance.*

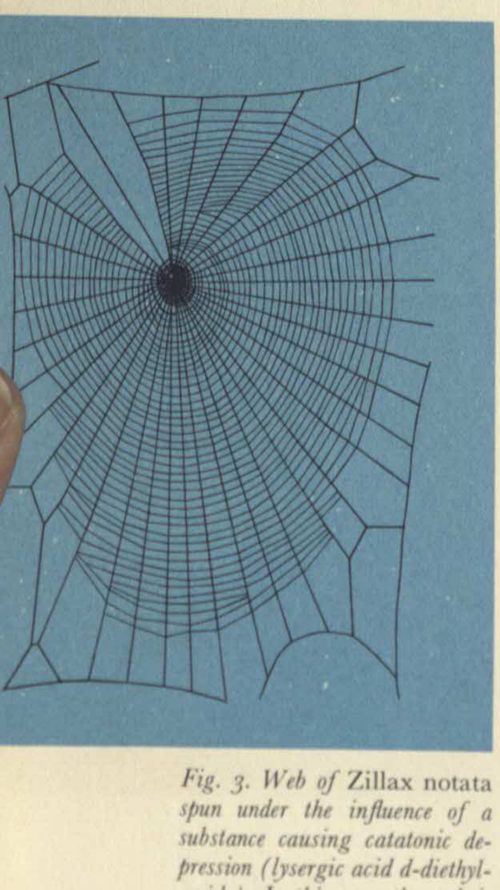

Fig. 3. Web of Zillax notata *spun under the influence of a substance causing catatonic depression (lysergic acid d-diethylamide). In this case the web is remarkably regular.*

this mistaken view results can be adduced which are misleading, particularly in considering such subtle integrations as are found in behaviour. If we think of the 'experimental neuroses' from which Pavlov expected so much in the way of understanding and treating human illnesses, we shall see why. Insufficient critical analysis or the making of superficial analogies may lead to the assumption that the various diseases which can be thus caused in cats, dogs or monkeys are the same as human neuroses. In fact, these neuroses have a different cause, are different in their psychological and biological structure, and have a different meaning.

From this point of view, animal behaviourism reverses the position of classical psychology and physiology, the auxiliary sciences of experimental medicine, and of general psychology. By its techniques and by a rich harvest of information, even by correction of its own hypotheses, it brings forward a new basis and new materials with which to build on it, and so opens new perspectives on man's knowledge of himself, and thus for his psychological treatment.

Methods and techniques of psychobiology

To observe and analyze a phenomenon is, contrary to what one might suppose, a very difficult and complex operation, for the simple reason that we are not merely registering instruments, not photographic apparatus, not, to use Hume's expression, 'blank sheets' on which experience has only to imprint itself. Information derived from neurophysiology, or from psychobiology, or from the development of the intellect, shows that we are active agents, so that all types of perception or experience require an activity on the part of the person who perceives or experiences. Thus we cannot say that any facts are pure or simple; all activity is developed by a method without which facts cannot be classified, or even perceived, as Auguste Comte and Claude Bernard showed. The methods and the intellectual framework of the classic sciences arose from the dualism of Descartes, to which we owe in particular not only the extraordinary developments in biology and physiology, but also a wide variety of hastily propounded problems whose solutions remain unsatisfactory.

Psychobiology is a reaction against the dualism of biology and psychology based on Cartesian principles; that is, on classic biology and physiology. This dualism tends to reduce psychology to physiology and so to eliminate all originality from psychology. Treatment has suffered on the rebound from this speculative Cartesian doctrine. Problems concerning the organic or psychological origin of mental disturbances, or the organic or psychological origin of psychosomatic illnesses, are in fact insoluble, originating, as they do, from the application of Cartesian theories and methods.

What are the facts that contributed to the present renewal of interest in the human sciences? They are the complementary use of observation—an inexhaustible source of discovery—and experimentation by which the facts may be analyzed. Before beginning to experiment, one must take time to look around, to ask questions about the phenomena with which one is dealing, and to consider them from all aspects. Work in the laboratory is, of course, essential, but it may lead one into the danger of losing the sense of integration and synthesis and thus to lose the very meaning of the phenomena of life.

The techniques of psychology are simultaneously instruments of investigation, diagnosis, and treatment. They include:

1. *Qualitative investigations,* which are the best known (mental tests, intelligence tests, tests of personality, activity, etc). These are becoming more and more indispensable and require careful handling;

2. *Bio-psychological* or psychophysical tests, such as electroencephalography, psychopneumography, psychocardiography, etc;

3. *Therapeutic* techniques, such as painless childbirth based on Pavlovian neurophysiology, or methods of relaxation (Schultz and Jacobson) which are useful in the treatment of psychosomatic disorders;

4. *Neurophysiological* techniques used on the conscious animal. The attachment of micro-electrodes to the central nervous system allows us to record the electrical activity of the animal's brain during various forms of behaviour or to induce more or less complete sequences of behaviour by electrical stimulation of the various regions of the brain.[1] One of these experiments is that of von Holst and von Saint Paul (1960) who, by local stimulation of the brain of the domestic fowl, were able to release a whole series of behaviour patterns. These included preening, attack, sexual behaviour, and care of the young. Almost every day physiology and neurophysiology extend our knowledge of the nervous system, in particular of those subcortical centres which, according to the level of development, are responsible either for a part or for

the whole of our instinctive behaviour. The differentiation between animals and man appears less and less conjectural.

Comparative ethology

1. This method gives us new data on the differential analysis of intelligence. One of the most remarkable discoveries of our time is the 'language' of bees. Karl von Frisch has shown that bees communicate with each other by means of dances (in circles or up and down) which are carried out on the vertical struts inside the hive. This language expresses in a symbolic way the direction of the sun by the upward movements, other horizontal directions being indicated by other movements. Worker bees who have been out exploring for food can even indicate to the others where a detour has to be made. For instance, in order to avoid a rock in the direct path they will indicate the direction in a straight line, and at the same time the total distance to the food, including the detour. They are also able to correct information which they have given to the other workers, so as to take account of the movement of the sun (during their exploratory flights the sun moves through the sky at a rate of 15 degrees per hour) so that information gathered at one time can be communicated correctly two hours later.

These experiments have opened an important chapter on comparative psychology. The bees' ability to resolve the problem of the detour is an example of intelligence. The 'language' of bees is a symbolic activity of which we know few examples apart from those afforded by man himself.

Von Frisch's work has an even wider interest, for it concerns not only psychology but also the pathological aspect of instinct and intelligence. Psychopharmacology uses invertebrates to study the effect of drugs on the central nervous system. Various psychological disturbances have been produced in the spider *Zillax notata* by the use of pervitin, caffeine, etc, and lysergic acid d-diethylamide, or LSD, has given us a 'schizophrenic' spider of catatonic type (figs. 1–3).

A sense of time is common to all living organisms. During the day migratory birds orientate their flight by means of the sun and at night by means of the stars. This orientation is not a simple psychological phenomenon; it seems to be under the control of intracellular mechanisms. A deeper knowledge of both the biological and the psychological elements of behaviour will lead to a better understanding of certain phenomena that are determined by factors at present partially unknown, such as, for instance, certain cyclic disturbances of behaviour which occur in the course of some psychoses.

2. Ethology yields a rich harvest of facts that give rise to new ideas which in turn throw fresh light on psychobiological diseases. Let us consider certain aspects of this:

(a) By the term *group effect* the biologist means that an individual, whatever may be its position in the range of the animal kingdom, cannot be considered in isolation from its companions in the group. For example, among the termites, anatomy, physiology, and psychology (social function) are conditioned by the group itself. Any new division of functions brings about anatomical and physiological changes in individuals.

The effect of society on human physiology is less well understood, but it is known that living in groups affects growth. It has been shown that the growth of children in towns is quicker than in the country (the difference is about 2 lb per annum). This probably has some relation to the well-known alertness of young town dwellers, and on the other side this probably also explains the pronounced atonia found in those who have undergone long terms of imprisonment.

(b) Trophallaxis is another fundamental social activity. Strictly speaking, this means a social exchange of nutriments. This idea, extended to man, throws a new light on many aspects of psychology, both normal and pathological, of which the interpretation has until now been confused.

Visual and tactile contacts between the individuals in a society are essential for the full development of the emotions. This has been observed in the pigeon. The complete development of the adult, which is marked in the male by the presence of the milky secretion of the crop gland, is a social phenomenon which does not occur in isolation. If the female cat is prevented from licking her body, she becomes a bad mother and takes no care of her kittens. Other experiments of the same type open new perspectives on the meaning of self-trophallaxis, the visual and tactile discovery that every living organism makes of its own body, and of the care which it gives it.

Auto-stimulation appears as an obligatory phase, a sort of apprenticeship which appears to be required if an individual is to be capable of making and receiving social contacts. In man the 'auto-erotic' discovery of oneself is a necessary condition and starting point for subsequent development towards the normal

Gibbons, which come from Malaya, give us very useful information about the phylogeny of man. They are the only primates which are monogamous and bipeds. They communicate with each other by means of a highly complex language. (Photo Lod, taken in the laboratory of M. Goustard, Faculté des Sciences de Paris).

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(1) *See the article by Herbert Jasper on 'The Electrical Activity of the Brain' in Volume 5 of* The Living Universe.

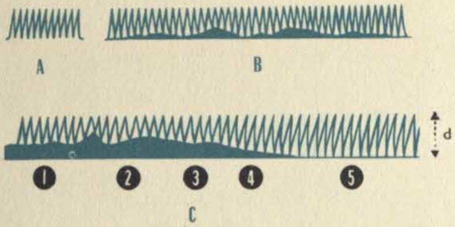


Fig. 4. Diagram showing variations of muscle tone in a normal person when awake (A), in an anxious person (B) and during induced sleep (C: 1–5). The base line is at first unstable (1), but becomes more regular when the person falls into a deep sleep (d). 2, injection of barbiturate. 3, the patient has a strange feeling. 4, beginning of sleep. 5, deep sleep.

adult 'allo-erotic' state. The idea of trophallaxis thus offers a unified viewpoint for numerous observations.

(c) The ideas of *dominance* and *subordination* are directly applicable to man. They give us a new insight into the place of instinct in man. Instinctive behaviour is difficult to change. Instincts are the stable mechanisms of behaviour. Halstead has shown that in their social relations most men keep to the tracks laid down by the 'dominance-subordination' system and this is in spite of neurophysiological structures (the hippocampus, according to Le Gros Clark) which allow us to integrate the working of the lower mechanisms of instinct with the unified control system of the intelligence.

From this there has resulted a humanity which so far has used its intelligence on the non-human environment, that of science and technology. But it has resulted also in the breaking up of society into units which exchange little information and whose interaction remains only slightly developed. In other words, there has been a lack of progress in humanizing social relations which has far-reaching consequences.

3. What is man? By giving us a better understanding of man himself, ethology has shed light on certain of his disorders and so has opened the way for appropriate treatment. As P. Grapin has clearly shown, the particular place occupied by man in the natural order of living creatures is not due exclusively to biological factors. Man does not occupy a privileged position merely on account of his upright posture, his possessing hands, his ability to talk, or by the absolute or relative volume of his brain. Nevertheless, he is the only living creature in which these three characters are found simultaneously and in relation to each other. These characters, whose relationship in activating one another constitutes the essential originality of man, do not make up any sort of biological mechanism. They are rather psychological characters, relational characters which have the following peculiarities: they are developed and reinforced by their use; they make man particularly adapted to life in relation to his environment and to other humans, and thus enable him not so much to adapt himself to this environment (as most animals do) but rather to adapt the environment to himself, and explain his capacity to transform himself.

The human being is the only organism capable of evaluating his own existence, of having a history. His health and illnesses are therefore profoundly different from those of animals. Only man is capable of using his mental potentialities to cure himself. In other words, his capability of transforming his external environment is correlated with his capability of transforming himself.

Psychobiological experimentation

The experimental study of the development of intelligence and emotion has widespread consequences. It renders it necessary to think again about the problem of psychological and biological relations, which form one aspect of the classical dualism of physical and mental make-up. In considering the fundamental effect of the external environment on the development and even on the formation of intelligence and emotion, we have to draw conclusions that affect both teaching methods and pathology. Psychobiological disturbances often go deep; they may be irreversible and influence the whole make-up of man; but the consequences of these considerations extend beyond the realms of disease into those of law and morality.

The structure of intelligence is not innate; it is formed during the extension of biological development. A line of behaviour, whether deployed in relation to the external environment or purely internal in the form of thought, appears as an adaptation. But, in contrast to organic adaptations, it is not only concerned with immediate relations, it also allows mediated relations between the subject and his environment. The whole development of intelligence, from the formation of an image (which allows us to go beyond immediate considerations by enlarging the field of adaptation and so permits us to bring to mind things beyond actual perception) to the function of the higher powers of reasoning, is a function of the greater scope of relations between the subject and the external world. Thus intelligence takes its place in biology and appears in its specificity.

The functional continuity between biology and the structures of intelligence does not exclude a heterogeneity of these structures. That which is found in other species is found also in man. As we pass from one level to another, it is not just another ring, another character that is added; the attainment of a new stage, in the case of the intelligence, goes hand in hand with the reorganization of the whole. In relation to biology the specificity of intelligence is that it gives us complete mobility and reversibility (logical reasoning enables us to combine the factors concerned in all possible combinations) which it is impossible to produce on the level of organic life. It follows that disturbances of intelligence may have their roots in biology.

Intelligence is rooted in neurophysiology. The nervous system is developed in relation to the organism and under the influence of the external environment. The correlation between the development of the intelligence and that of the nervous system does not mean that there is a parallelism between the two. The nervous system only determines the extent of the possibilities that can be used by the intelligence at any given moment of maturation. Even when it needs the intervention of distinct nervous structures, a new form of behaviour never appears discontinuous and can be explained partly in terms of those which preceded it. It follows that a disease affecting the intelligence cannot be explained wholly in terms of neurological disturbances.

The role played by the external environment—in particular, the social environment—is essential to the development both of the intellect and its diseases. It is so fundamental that supporters of Pavlov's theory of the conditioned reflex have upheld the idea of an essentially exogenous origin of higher mental activity. The social environment, and more exactly, the family environment can exert an influence on biological development. It has recently been shown that some men have a feminine sex-chromosome make-up. This does not, however, influence their sexual tendencies. From this it might be said that it is the family environment that brings about the sexual development of the individual.

The relationship between the mother and her infant are essential for both the physiological and the psychological development of the child. One can truly speak of the 'symbiotic pair' formed by the mother and the infant, to show the extremely close link which exists between mother and child. The first relationships of the human being, those with his mother, even before birth, are effected through psychophysiological conditioning, so that even before the development of intelligence, the emotional state of the mother has repercussions on the child and condition it in its physiological, psychological, and emotional development.

The mother may suffer from various psychological upsets. These may be a hostility, more or less conscious, or variations of mood, alternating periods of tenderness and hostility, etc. Spitz (1958) showed that 37 per cent of children suffering from a severe lack of affection die before the age of three years, as compared with no deaths, except from other causes, in children given normal parental love. Less marked lack of parental affection may give rise to many types of psychosomatic disorders, vomiting, respiratory troubles, or colic, if the mother is over-anxious, etc.

Lack of affection may lead to a deterioration in all aspects of personality. In certain cases this had led to diminished psychomotor development of as much as 45 per cent compared with that which is normal. Those who survive become delinquents.

Delinquency has multiple causes and their investigation is still far from complete. People whose relations with their mother have been severely disturbed may very well become incapable of normal relationships with other human beings. Then, according to Spitz, they act in the only way left open to them; that is, they turn to violence and the destruction of the social order of which they have been the victims: from being unloved infants they become adults full of hate. These facts are as important for treatment as they are for educationists and parents. The figures show the enormous responsibility of those who bring a new human being into the world.

But, although the external environment may be essential for the development of intelligence and emotions, it is not enough to explain the whole mechanism of mental formation or maladjustment. Neurophysiology, the psychobiology of growth and the analysis of inborn behaviour (Lorenz) all lead one to the same conclusion: that the subject does not only receive passively and react automatically to the stimuli which he receives from his environment. The animal builds up its environment in conformity with its own organization; man is a subject, that is, an agent of integration, who gives his own meaning to the adaptational functions of his organism in relation to his environment.

Psychobiology provides us with fundamental data on man. A human being is an indissoluable biological and psychological unity, with his two poles constantly interacting. All his diseases have, therefore, a double aspect, psychological and biological, with differences in emphasis.

The higher activities of man are the result of a development that can be helped by environmental conditions, or upset, perhaps irremediably. This fact is of particular interest to all educationalists, who have a decisive role to play in the future happiness or unhappiness of those in their charge.

HISTORICAL NOTES

1879 FIRST STAGE

Psychology, an experimental science. HELMHOLTZ, WUNDT, EBBINGHAUS, reduction of psychology to physiology and physics. Psychophysics, WEBER and FECHNER. The same tendency in the application of cybernetics to psychology.

1920 SECOND STAGE

To the behaviourism of WATSON, KUO, and LOEB was added the conditioned-reflex theory of Pavlov which reduces psychology to reflexes and tries to reconstruct psychological life solely in terms of external environment.

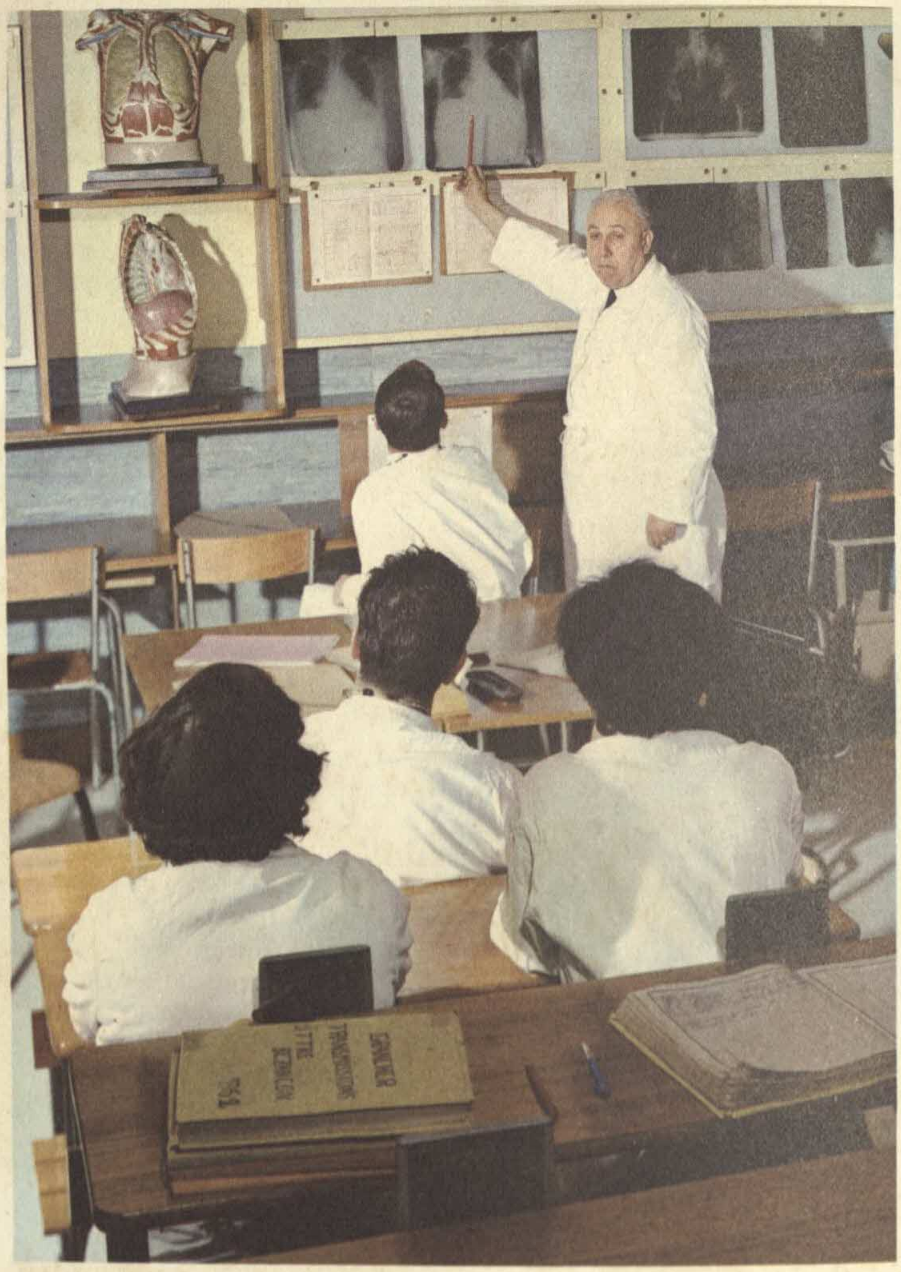
1930 THIRD STAGE

Gestalt psychology (WERTHEIMER, KOEHLER, and LEWIN) reacted against the association theory of previous authors. Foundation of psychology on the idea of form which is not reducible to its elements. Application to neurology (GOLDSTEIN).

FOURTH STAGE

Re-introduction of the 'subject' into the sciences of man. VON WEISZAECKER works on the physiological aspect. LORENZ and the zoo-psychologists work on instinct. PIAGET deals with the indissociable interaction of subject and object in the development of intelligence. Behaviour has a direction and a significance, psychology cannot be reduced to physics.

We saw at the beginning of this book what complicated tables of results could be constructed from the multiple investigations of all sorts which are nowadays carried out in cases of serious disease. From such tables we have to produce a diagnosis which is related to life. For this reason, the various doctors treating the patient get together, as is shown in these photographs, to discuss the patient's case. After outlining the development and the general picture of the disease, with the help of radiographs, charts, temperature records, etc (above) the doctor draws his conclusions as to diagnosis and prescribes the form of treatment (right). Then the general conclusions that arise are discussed with the patient herself (below). These are phases in the round-table discussion which are becoming more emphasized in modern medicine and upon which medicine must depend for maximum precision and efficiency. (Photos Lod).



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